

# Multiple-scale stochastic processes: decimation, averaging and beyond

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## Abstract

The recent experimental progresses in handling microscopic systems have allowed to probe them at levels where fluctuations are prominent, calling for stochastic modeling in a large number of physical, chemical and biological phenomena. This has provided fruitful applications for established stochastic methods and motivated further developments. These systems often involve processes taking place on widely separated time scales. For an efficient modeling one usually focuses on the slower degrees of freedom and it is of great importance to accurately eliminate the fast variables in a controlled fashion, carefully accounting for their net effect on the slower dynamics. This procedure in general requires to perform two different operations: decimation and coarse-graining. We introduce the asymptotic methods that form the basis of this procedure and discuss their application to a series of physical, biological and chemical examples. We then turn our attention to functionals of the stochastic trajectories such as residence times, counting statistics, fluxes, entropy production, etc. which have been increasingly studied in recent years. For such functionals, the elimination of the fast degrees of freedom can present additional difficulties and naive procedures can lead to blatantly inconsistent results. Homogenization techniques for functionals are less covered in the literature and we will pedagogically present them here, as natural extensions of the ones employed for the trajectories. We will also discuss recent applications of these techniques to the thermodynamics of small systems and their interpretation in terms of information-theoretic concepts.

**Keywords:** Markov processes, Diffusive processes, Multiscale methods, Irreversibility, Stochastic functionals

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## 1. Motivations and examples: Stochastic processes with multiple time scales.

When modeling a process one of the most challenging issues to address is to determine which variables are the fundamental ones that characterize the system and which ones are just details that can be safely disregarded. Once these relevant variables are identified, one would like to have a dynamic description of their evolution.

Neglecting the inessential processes is crucial for providing a neat, useful description of the considered phenomena. Several methods are available to reduce the complexity of involved systems especially when the scales on which the various interacting processes take place are different. The use of stochastic formalisms in modeling physical, chemical or biological processes is on this line of reasoning. Rather than following the microscopic erratic evolution of some processes their net contribution is accounted for by a random term that preserves the relevant statistical properties that affect the overall behavior of the system.

Think for instance of Brownian motion: the erratic motion of a mesoscopic particle immersed in a fluid. A complete description would require the solution of the equation of motion of the Brownian particle and of those of the many fluid particles with which it collides. Modeling the collisions as a white noise term with an amplitude that depends on the physical properties of the fluid and the particle greatly simplifies the formalism and yet provides an excellent description of the statistics of the phenomenon.

Similarly, when considering chemical reactions [1], a probabilistic treatment in terms of a chemical master equation provides an efficient formalism which is immensely simpler than the the solution of the complete molecular dynamics of the reagents.

Once stochastic systems are taken as the starting models their complexity can also be reduced. Various methods exist to extract the relevant features form large stochastic systems involving several components. Here, we focus on the case in which different time scales are involved. This provides a 'natural' distinction between the different processes.

A paradigmatic example is again given by Brownian motion, and namely by the strong friction (overdamped) limit of Langevin-Kramers dynamics, in which the velocity degrees of freedom very rapidly converge to equilibrium. As discussed above, the collisions with the fluid particles can be described as a noisy force acting on the particle so that the system obeys the following set of equations

$$\begin{aligned} \dot{\mathbf{X}}_t &= \mathbf{V}_t \\ m \dot{\mathbf{V}}_t &= -\gamma \mathbf{V}_t + \sqrt{2k_B T \gamma} \boldsymbol{\xi}_t \end{aligned} \quad (1)$$

where  $\boldsymbol{\xi}_t$  is a Gaussian, zero-mean white noise, i.e.  $\langle \xi_i^t \xi_j^{t'} \rangle = \delta^{ij} \delta(t - t')$ ,  $T$  is the fluid temperature,  $k_B$  the Boltzmann constant and  $\gamma$  the viscous friction coefficient. According to Stokes law we have that  $\gamma = 6\pi\eta a$  where  $a$  is the radius of the Brownian particle and  $\eta$  the fluid dynamic viscosity. At the microscale friction dominates the motion. Indeed, a spherical particle of radius  $a = 1 \mu m$  traveling at a speed of  $50 \mu m s^{-1}$  in water experiences such a strong damping that if no external force is applied it would stop in less than a microsecond ( $\sim m/\gamma$ ) and travel only  $0.1 \text{ \AA}$  [2]. This shows how inertia plays a negligible role in the dynamics and how relaxation takes place on a fast time-scale. One is therefore tempted to discard it altogether and to revert to an Aristotelian description of the motion. We would then have a description involving only the positional degrees of freedom and neglecting the velocity ones. This is indeed possible and goes under the name of overdamped approximation

$$\dot{\mathbf{X}}_t = \sqrt{2k_B T / \gamma} \boldsymbol{\xi}_t \quad (2)$$

and provides an accurate description of the process on time scales longer than the relaxation ones ( $t \gg m/\gamma$ ).

In biology there are usually many more time scales on which intertwined processes take place. Just to mention an example consider the cell response to a change in the environment. Such response involves several subsequent reactions starting from the detection of the signal by membrane receptors, which takes a fraction of a second, then triggering the signaling cascades, on the minutes time-scale, finally resulting in the organization of the suitable transcriptional response, which takes place in several hours [3].

Also chemistry is rich in multiple time-scale reaction networks where the characteristic times of the single reactions may span several orders of magnitudes. Such networks are hard to describe in detail and the presence of processes which are much faster than others makes simulations via the Gillespie algorithm [4] computationally very demanding. Indeed, one has to simulate a large amount of fast events before the slow ones (which usually are the

relevant ones) start taking place. When fast and slow reaction are treated on the same footing the procedure cannot be efficient (see e.g. [5]).

One would rather aim at describing the dynamics on the slower time scales not by fully following the details of the fastest processes but just accounting for their overall contributions to the slower processes. Can this be done in a systematic way without making recourse to uncontrolled approximations ?

Asymptotic methods provide indeed the appropriate tool to derive systematically the slow dynamics by consistently eliminating/grouping the fast degrees of freedom in order to obtain an effective Markov process that describes the transitions between suitably defined “slow states” [6]. For instance, the overdamped approximation of the Langevin-Kramers dynamics is consistent with the adiabatic elimination of the velocity degrees of freedom.

We will provide a detailed, systematic description of asymptotic methods for both discrete and diffusive Markov processes in the first part of this report. Examples from simple biochemical networks and processes on more complex graphs will be presented to show how to apply these techniques. For diffusive processes, we will discuss applications to population genetics and to Brownian motion in inhomogeneous fluid environments.

A much less explored question is what can possibly be said about observables that depend on the trajectories of the system. These include but are not limited to: residence and first-passage times, counting statistics, fluxes, entropy production, etc. Is it possible to obtain a correct description of the slow evolution of these quantities ? What level of knowledge about the details of the fast dynamics is required ? In the second part of this report we will address these questions by extending the asymptotic methods presented in the first part.

A specific instance of this problem that deserves special attention is entropy production. Systems that are amenable to a stochastic modeling admit indeed a thermodynamic description where fluctuations play a prominent role (see [7, 8, 9, 10, 11, 12, 13] for the definitions). Such stochastic thermodynamic framework has proven to be effective in the description of small systems involving few components studying the energy exchanges accompanying their evolution.

The problem of deriving an effective thermodynamic description for slow dynamics has been addressed in several works (see e.g. [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]). In section 4.3 and 5.2 and we will address this problem and show by the application of asymptotic techniques that under quite general non-equilibrium conditions it is not possible to give a correct description of thermodynamics just in terms of the slow variables. Indeed, neglecting altogether the fast processes, while it leads to consistent equations for the effective dynamics, can nevertheless overlook the irreversibility of some processes compromising the thermodynamic interpretation of the effective system. (In order to reassure the reader, we anticipate that detailed balance will be shown to be sufficient to warrant consistency between the microscopic and the macroscopic thermodynamics.).

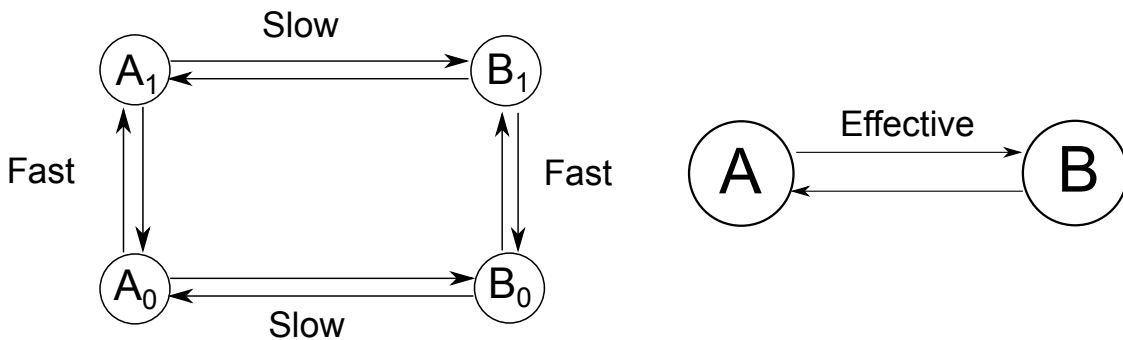


Figure 1: Left: Full dynamics involving two time scales. Right: Effective dynamics

One can already get an intuition of this issue by considering the toy system sketched in figure 1 where we have four states and four transition channels. State  $A$  rapidly switches between two possible conformations which can slowly convert to a state  $B$ . Also state  $B$  oscillates between two states. Given the difference in the transition rates, by looking at the system on slower scales (or with low temporal resolution), one would not distinguish the substates and basically observe the effective dynamics involving  $A$  and  $B$ . This description provides a good approximation of the dynamics. However, thermodynamically the full description and the effective one are crucially different. The complete one can feature cycles at the steady state whereas the reduced one, displaying only two states, cannot. This implies that the

full system may be in a non-equilibrium steady state and that, on the contrary, for the effective system stationarity must correspond to equilibrium.

As embarrassingly simple as this example may seem, it nonetheless has the merit of highlighting the risks in defining thermodynamics starting from the effective dynamics without being aware of what the eliminated details are. At the same time, by showing what are the details of the fast processes that must not be neglected we can provide a tool for consistently deriving the effective description of entropy production.

We close this introduction with a disclaimer. This report makes no attempt at providing an exhaustive review of previous results in the subject. Rather, it aims at providing a personal viewpoint with the hope that the reader will find in it a systematic way to approach these problems and gain some working knowledge about the relevant techniques.

# Part I

## Dynamics

### 2. Discrete Markov chains

*The question.* Is it possible to exploit time-scale separation to obtain an effective Markovian dynamics on a reduced state space? Under what conditions? What are the relevant properties of the initial system that have to be kept into account?

Several processes in physics [25], biology [26, 27] and chemistry [28] are best modeled by continuous-time Markov chains. Studying the complete dynamics of complex Markovian networks becomes easily unfeasible as the number of states increases. It is then of great importance to attempt to reduce such complexity by exploiting the structure of the network. This can be achieved by identifying groups of states that share some features and deriving an effective dynamics between such groups or by directly eliminating some transient states based on their low probability of occupation. However, in general, the resulting dynamics between blocks will not be Markovian and the waiting times for jumps will follow a phase type distribution reflecting the Poissonian transitions between the internal states. Systems featuring separated time scales are of particular interest. On the one hand, they pose serious issues for simulation purposes (e.g. via the Gillespie algorithm [4]) as one has to generate a large number of the fast events before observing the slow ones. Such problem is often referred to as stiffness and has attracted considerable interest [29, 5, 30, 31, 32, 33, 34, 35, 36, 37, 38, 14, 39, 22, 40]). On the other hand, they suggest a natural structure for model reduction. The reduction may be achieved via decimation: the elimination of transient states that rapidly relax to vanishing probabilities (see e.g. [37, 35, 36, 39]). The time separation may also allow to define blocks of rapidly equilibrating states which then undergo a Markovian effective dynamics on slower time scales, a procedure which we shall refer to as averaging [30, 14, 22, 6]. In the present section we shall detail how a multiple-scale approach can be applied to systematically address systems presenting two widely separated time scales. This approach extends the one given in Refs. [6, 22]. As examples we will provide applications of the general procedures to the problem of studying the fluctuations of protein numbers in cells, sensing and chemical kinetics.

#### Preliminaries

Consider a continuous-time Markov chain displaying transitions between discrete states with given rates. In general, the evolution of such systems is described by a master equation:

$$\frac{dp_m^i}{dt} = \sum_j (K_j^i p_m^j - K_i^j p_m^i) \quad (3)$$

where  $p_m^i(t, t')$  denotes the probability of being in state  $i$  at time  $t$  having started from state  $m$  at time  $t'$  and  $K_j^i$  the transition rate from state  $j$  to state  $i$ .<sup>1</sup> In compact notation

$$\frac{d\mathbf{p}}{dt} = (\mathbf{K} - \text{diag}(\mathbf{1}^\dagger \mathbf{K})) \mathbf{p} = \mathbf{L} \mathbf{p} \quad (4)$$

where  $\mathbf{1}^\dagger$  is a row vector with all entries equal to 1 and, consequently,  $\text{diag}(\mathbf{1}^\dagger \mathbf{K})$  is a diagonal matrix with the elements  $i, i$  given by the exit rate from  $i$ :  $e_i = \sum_j K_i^j$ .

#### Time-scale separation

Let us now turn our attention to systems with transition rates of different magnitude. For the sake of clarity we shall discuss the case in which the rates belong to two different classes, a slow one and a fast one. To make such

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<sup>1</sup>Note that in this section, whenever dealing with discrete processes, we assume no implicit summation for the repeated indices.

separation explicit we will denote the ratio between slow and fast rates as  $\epsilon$ . The corresponding master equation then takes the following form:

$$\frac{d\mathbf{p}}{dt} = \epsilon^{-1}\mathbf{M}\mathbf{p} + \mathbf{L}^{(0)}\mathbf{p} \quad (5)$$

where  $\mathbf{M}$  generates the fast process and  $\mathbf{L}^{(0)}$  the slow one<sup>2</sup>. Both  $\mathbf{M}$  and  $\mathbf{L}^{(0)}$  conserve probability:  $\mathbf{1}^\dagger \mathbf{M} = \mathbf{1}^\dagger \mathbf{L}^{(0)} = 0$ . Given a pair of states, a transition in one direction can be much faster than its reversed one. This means that for such states we will have  $M_i^j \neq 0$  but  $M_j^i = 0$ . As a consequence, the directed graphs associated to the fast and slow transitions may not be strongly connected. Recall that a directed graph is said to be strongly connected if, for any given pair of its vertices (e.g.  $i$  and  $j$ ), there is a path connecting them in each direction (e.g.  $i \rightarrow \dots \rightarrow j, j \rightarrow \dots \rightarrow i$ , it need not be the same path).

As anticipated in the introduction, the existence of different time scales can justify certain approximations (which become exact in the limit of infinite time-scale separation, *i.e.*,  $\epsilon \rightarrow 0$ ) that simplify considerably the dynamics. The kind of simplification and its extent depends mostly on the structure of the fast connections and can be determined by inspection of the network composed solely of the fast transitions, *i.e.*, by the algebraic properties of  $\mathbf{M}$ . If the fast network is strongly connected, it is not possible to exploit the time-scale separation to reduce the complexity of the complete system by defining some suitable effective Markovian system. On the contrary, if the graph is not strongly connected,  $\mathbf{M}$  is a reducible matrix and it is possible to express it in its normal form, *i.e.*, as a lower block triangular matrix by permutations of its rows and columns. Each block along the diagonal represents a strongly connected component. The network composed of the strongly connected components and the transitions across them is called a condensation of the graph and it is a directed acyclic graph. Inspection of the graph condensation allows to identify the blocks that will take part in the effective dynamics. They are the ones with no outgoing transitions: the sinks of the directed acyclic graph. Indeed, the blocks with outgoing connections do not conserve probability but "leak" it on the fast scale leading to a vanishing probability of occupation and will not be present in the effective description. A transient block is characterized by a negative sum of its rows, indicating that it is not conserving probability. The elimination of transient blocks (or states) is often referred to as decimation. Summarizing, we have the following recipe for simplifying the dynamics in presence of a time-scale separation when the graph composed of the fast transitions is not strongly connected:

1. Inspect if the fast transitions represent a strongly connected graph.
2. Identify the blocks, *i.e.*, the strongly connected components of the graph associated to  $\mathbf{M}$  (the fast transitions generator)
3. Eliminate the blocks that do not conserve probability, *i.e.*, keep only sinks of the graph condensation
4. Derive the effective dynamics between the remaining blocks on the slower time-scale

Notice that for the first three steps, only knowledge about the fast transitions is required. The asymptotic approach we present allows to eliminate the rapidly emptying blocks and to derive an effective dynamics between the remaining ones. We shall present this general procedure, via a general example where, for the sake of simplicity we do not consider the dependence on the initial state so that the probability is simply a vector  $p^i$ .

### 2.1. General example

Consider the Markov chain described in figure 2 where the solid lines represent fast rates and the dashed ones slow rates. The generators read respectively:

$$\mathbf{M} = \begin{pmatrix} -F_1^2 & F_2^1 & F_3^1 & 0 & 0 & 0 \\ F_1^2 & -F_2^1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -(F_3^1 + F_3^4 + F_3^5) & F_4^3 & 0 & 0 \\ 0 & 0 & F_3^4 & -F_4^3 & 0 & 0 \\ 0 & 0 & F_3^5 & 0 & -F_5^6 & 0 \\ 0 & 0 & 0 & 0 & F_5^6 & 0 \end{pmatrix} \quad (6)$$

<sup>2</sup>Note that the time-scale separation is accounted for by the parameter  $\epsilon$  and that  $\mathbf{M}$  and  $\mathbf{L}^{(0)}$  are of the same order of magnitude

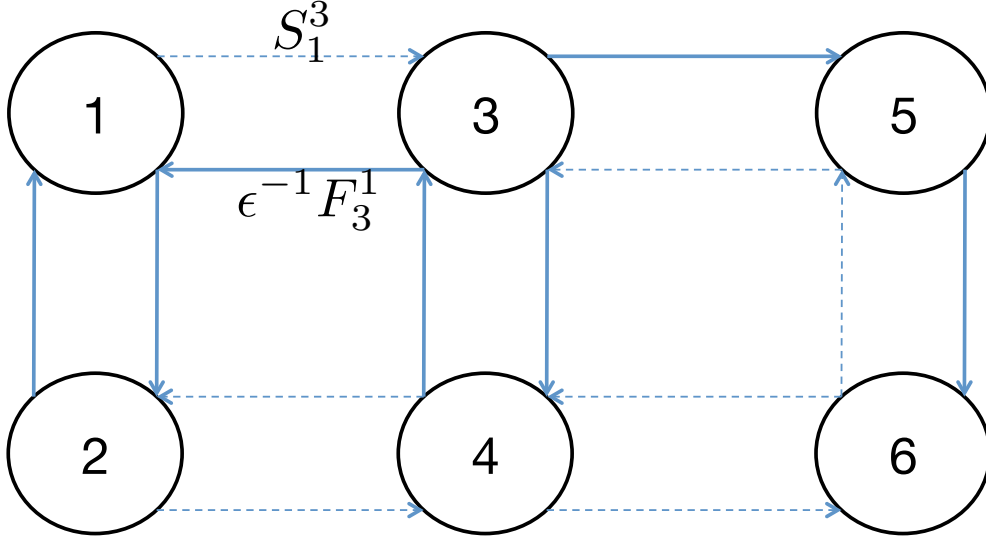


Figure 2: Continuous-time Markov chain involving 6 states. The dashed lines represent transitions occurring at low rates whereas the solid ones fast transitions.

and

$$L^{(0)} = \begin{pmatrix} -S_1^3 & 0 & 0 & 0 & 0 & 0 \\ 0 & -S_2^4 & 0 & S_4^2 & 0 & 0 \\ S_1^3 & 0 & 0 & 0 & S_5^3 & 0 \\ 0 & S_2^4 & 0 & -(S_4^2 + S_4^6) & 0 & S_6^4 \\ 0 & 0 & 0 & 0 & -S_5^3 & S_6^5 \\ 0 & 0 & 0 & S_4^6 & 0 & -(S_6^4 + S_6^5) \end{pmatrix} \quad (7)$$

where the  $F$  and  $S$  are of the same order (the bookkeeping parameter  $\epsilon$  takes care of their magnitude difference) and used to label respectively fast and slow transition rates.

*Step 1.* By inspection of the network involving fast transitions only (solid lines in figure 2) we see that it is not strongly connected.

*Step 2.* Indeed, the matrix  $M$  of eq. 6 is reducible and, by permutation of its states (to (3, 4, 5, 1, 2, 6)), it can be written as a block triangular matrix

$$\tilde{M} = \left( \begin{array}{cc|cc|c} -(F_3^1 + F_3^4 + F_3^5) & F_4^3 & & & \\ F_3^4 & -F_4^3 & & & 0 \\ \hline F_3^5 & 0 & -F_5^6 & & \\ F_3^1 & 0 & 0 & -F_1^2 & F_2^1 \\ 0 & 0 & 0 & F_1^2 & -F_2^1 \\ \hline 0 & 0 & F_5^6 & 0 & 0 & 0 \end{array} \right) \quad (8)$$

showing the underlying block structure. Four blocks can be identified: the one including states 3, 4 which we shall name  $b$ , the one with 1, 2 called  $a$  and two blocks involving single states, 5 and 6 that we will name respectively  $c$  and  $d$ . They represent the strongly connected components of the graph describing the fast transitions.

*Step 3.* The condensation of the fast connections graph is shown in figure 3. Blocks  $b$  and  $c$  have outgoing fast transitions whereas blocks  $a$  and  $d$  are sinks of the condensation. Indeed, summing the first two lines of the fast transition matrix (8), one sees that block  $b$  does not conserve probability and will therefore relax to a vanishing probability of occupation on fast time scales. Also block  $c$  (state 5) "leaks" probability. Hence, the blocks  $b$  and  $c$  can



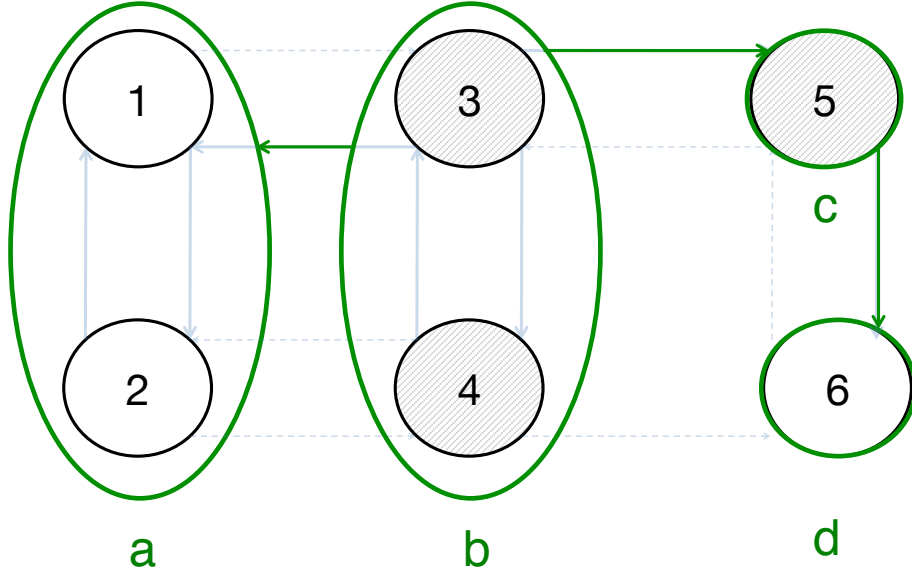


Figure 3: Condensation of the fast transitions graph of figure 2. Four blocks (strongly connected components) are identified and shown in green. The fast transitions across blocks are highlighted with green arrows. Only blocks *a* and *d* are sinks: they have no fast outgoing transitions.

be eliminated from the effective description. On the contrary, blocks *a* and *d* conserve probability and will be part of the effective dynamics on the slow scales.

*Step 4.* In order to determine the effective dynamics between the surviving blocks we will systematically exploit the time-scale separation employing a multiple scale technique (see e.g. [6]). The first key idea is to formally introduce the fast time-scale  $\theta = \epsilon^{-1}t$  on which the rapid processes are expected to equilibrate. The second one is to develop the probability as  $p = p^{(0)} + \epsilon p^{(1)} + \dots$ . Applying such expansions to eq. (5), one gets a hierarchy of equations. At order  $\epsilon^{-1}$  the system reads

$$\frac{dp^{(0)}}{d\theta} = Mp^{(0)}. \quad (9)$$

After the initial rapid relaxation (requiring a time  $O(\epsilon)$ ) we obtain a stationary solution

$$Mp^{(0)} = 0 \quad (10)$$

where  $p^{(0)}$  is a positive column vector belonging to the right nullspace of the matrix  $M$ . The presence of two blocks conserving probability in  $M$  implies that the nullspace has multiplicity 2. It is spanned by

$$w^a = \begin{pmatrix} w^{a_1} \\ w^{a_2} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad w^d = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ w^{d_6} \end{pmatrix} \quad (11)$$

where  $w^i$  is a normalized equilibrium solution of the block  $M_i$ :

$$w^{a_1} = \frac{F_2^1}{F_2^1 + F_1^2} \quad w^{a_2} = \frac{F_1^2}{F_2^1 + F_1^2} \quad w^{d_6} = 1. \quad (12)$$

At first order then, one finds the probability to be

$$p^{(0)} = \phi_a w^a + \phi_d w^d \quad (13)$$

where  $\phi_i$  is a generic function obeying the normalization  $\sum_i \phi_i = 1$ . We have then split the first order probability into two factors: the probability of being in a block  $\phi_i$  and the equilibrium (with respect to the fast dynamics) probability of being in a state conditional on a given block. The equation at order  $\epsilon^0$  reads

$$\frac{dp^{(1)}}{d\theta} + \frac{dp^{(0)}}{dt} = M p^{(1)} + L^{(0)} p^{(0)} \quad (14)$$

and, after the fast relaxation,

$$M p^{(1)} = \frac{dp^{(0)}}{dt} - L^{(0)} p^{(0)}. \quad (15)$$

According to the Fredholm alternative, eq. (15) is solvable only if its RHS is orthogonal to the left nullspace of  $M$ . Such nullspace has the same dimension of the right one (2) and, for this example, it is spanned by:

$$v^a = \left( 1, 1, \frac{F_3^1}{F_3^1 + F_3^5}, \frac{F_3^1}{F_3^1 + F_3^5}, 0, 0 \right) \quad v^d = \left( 0, 0, \frac{F_3^5}{F_3^1 + F_3^5}, \frac{F_3^5}{F_3^1 + F_3^5}, 1, 1 \right) \quad (16)$$

where the vectors are chosen to be biorthonormal to the ones spanning the right nullspace. The entries of such vectors have a clear interpretation in terms of probability of being absorbed by a given block. The entries  $v_i^a$  are the probability of being absorbed in block  $a$  having started in state  $i$ . So, for example, the first two entries of  $v^a$  indicate the probability of being absorbed in block  $a$  having started from  $a$ , namely from 1 and 2, which is equal to one. The third and fourth entry are the probability of ending in  $a$  having started in  $b$ , from 3 and 4, and are given by the probability of choosing a transition from state 3 to state 1 rather than one to state 5:  $\frac{F_3^1}{F_3^1 + F_3^5}$ .

A generic vector in the left nullspace can be written as

$$\hat{p}^{(0)} = \hat{\phi}_a v^a + \hat{\phi}_d v^d \quad (17)$$

for generic  $\hat{\phi}_i$ . The solvability condition then requires that:

$$\hat{p}^{(0)} \frac{dp^{(0)}}{dt} - \hat{p}^{(0)} L^{(0)} p^{(0)} = 0 \quad (18)$$

which, owing to the biorthonormality, reduces to the set of two equations:

$$\begin{aligned} \hat{\phi}_a \left\{ \frac{d\phi_a}{dt} - v^a L^{(0)} (\phi_a w^a + \phi_d w^d) \right\} &= \hat{\phi}_a \left\{ \frac{d\phi_a}{dt} - \frac{1}{F_3^1 + F_3^5} [F_3^1 S_6^4 \phi_d - F_3^5 (w^{a_1} S_1^3 + w^{a_2} S_2^4) \phi_a] \right\} = 0 \\ \hat{\phi}_d \left\{ \frac{d\phi_d}{dt} - v^d L^{(0)} (\phi_a w^a + \phi_d w^d) \right\} &= \hat{\phi}_d \left\{ \frac{d\phi_d}{dt} + \frac{1}{F_3^1 + F_3^5} [F_3^1 S_6^4 \phi_d - F_3^5 (w^{a_1} S_1^3 + w^{a_2} S_2^4) \phi_a] \right\} = 0. \end{aligned} \quad (19)$$

Since such condition has to be satisfied for any choice of  $\hat{\phi}_i$  the terms inside braces must equal zero giving what is the effective dynamics between the surviving blocks:

$$\begin{aligned} \frac{d\phi_a}{dt} &= (K_{eff})_d^a \phi_d - (K_{eff})_a^d \phi_a \\ \frac{d\phi_d}{dt} &= (K_{eff})_a^d \phi_a - (K_{eff})_d^a \phi_d \end{aligned} \quad (20)$$

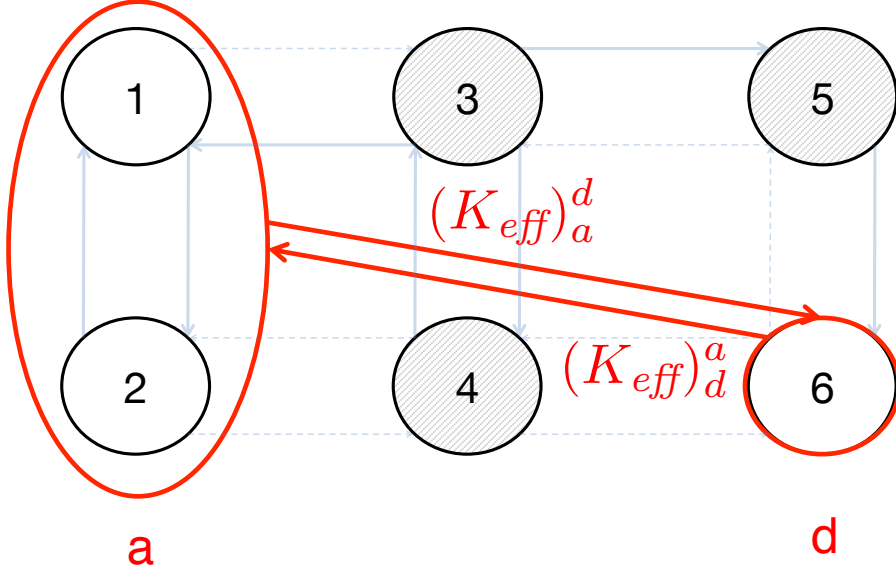


Figure 4: Effective process corresponding to the Markov chain described in fig. 2. The dynamics takes place between block  $a$  (consisting of 2 states) and block  $d$  (a single state) with rates  $(K_{eff})_d^a$  and  $(K_{eff})_a^d$ . State 3, 4, 5 have a vanishing probability at first order and are therefore decimated from the system. Within block  $a$  the probability of being in state 1 and 2 are given by the steady state solution  $w^{a1}$  and  $w^{a2}$  as in eq. (12).

with the effective rates

$$\begin{aligned} (K_{eff})_d^a &= v^a \mathbf{L}^{(0)} w^d = -v^d \mathbf{L}^{(0)} w^d = \frac{F_3^1}{F_3^1 + F_3^5} S_6^4 \\ (K_{eff})_a^d &= v^d \mathbf{L}^{(0)} w^a = -v^a \mathbf{L}^{(0)} w^a = \frac{F_3^5}{F_3^1 + F_3^5} (w^{a1} S_1^3 + w^{a2} S_2^4). \end{aligned} \quad (21)$$

The fact that  $v^a \mathbf{L}^{(0)} w^d = -v^d \mathbf{L}^{(0)} w^d$  is ensured by  $v_a + v_d = (1, \dots, 1)$  and  $\sum_i L_{ij}^{(0)} = 0$ . Equation (18) then identifies the effective dynamics which can be expressed as (see fig. 4)

$$\frac{d\phi}{dt} = (\mathbf{L}^{(0)}_{eff}) \phi \quad (22)$$

where the dimension of  $\phi$  is given by the number of blocks that conserve probability (2 in this example). The shown procedure has allowed us to reduce the initial network involving all states (6) to a much smaller one in two steps: decimating the blocks not conserving probability (state 3, 4, 5) and averaging by grouping the states that rapidly reached equilibrium (state 1 and 2) in a block. Before proceeding further, let us present an alternative, equivalent derivation of the effective dynamics which highlights the connection with the decimation procedure discussed, for example, in [37, 40]. Let us rearrange our states by ordering first the blocks with vanishing probabilities (transient) and then the ones conserving probability (recurrent). Our probability vectors then read:  $p = (p_T, p_R)$  where  $p_T$  denotes the probability of the transient states and  $p_R$  the ones of the recurrent states. The order of the example (3, 4, 5, 1, 2, 6),

is already in this form. However, in general, listing first the vanishing states is more restrictive than simply ordering the matrix in block triangular order. By definition  $p_T^{(0)} = (0 \dots 0)$  and for the chosen example  $p_R^{(0)} = (w^{a_1} \phi_a, w^{a_2} \phi_a, \phi_d)$ . The fast transition matrix can be written as in eq. 8 now highlighting

$$\tilde{M} = \begin{pmatrix} M_{T \rightarrow T} & 0 \\ M_{T \rightarrow R} & M_{R \rightarrow R} \end{pmatrix} \quad (23)$$

where  $M_{T \rightarrow T}$  contains the transition within and between transient blocks,  $M_{T \rightarrow R}$  the ones from the transient ones to the recurrent ones and  $M_{R \rightarrow R}$  within the recurrent blocks, being block diagonal. Then the equation at order  $\epsilon^0$  (15) can be written separately for the transient and recurrent components:

$$M_{T \rightarrow T} p_T^{(1)} + L^{(0)}_{R \rightarrow T} p_R^{(0)} = 0 \quad (24)$$

$$L^{(0)}_{R \rightarrow R} p_R^{(0)} + M_{T \rightarrow R} p_T^{(1)} + M_{R \rightarrow R} p_R^{(1)} = \frac{d}{dt} p_R^{(0)} \quad (25)$$

and, upon solution of the first one,

$$(L^{(0)}_{R \rightarrow R} - M_{T \rightarrow R} (M_{T \rightarrow T})^{-1} L^{(0)}_{R \rightarrow T}) p_R^{(0)} + M_{R \rightarrow R} p_R^{(1)} = \frac{d}{dt} p_R^{(0)}. \quad (26)$$

Multiplying by the left eigenvectors spanning the null space of  $M_{R \rightarrow R}$  we obtain the effective equation. Since each block on the diagonal of  $M_{R \rightarrow R}$  is a stochastic matrix the eigenvalues are composed of blocks of 1 and the multiplication corresponds to summing over the states within the recurrent blocks. The effective equation then reads

$$\overline{(L^{(0)}_{R \rightarrow R} - M_{T \rightarrow R} (M_{T \rightarrow T})^{-1} L^{(0)}_{R \rightarrow T})} \phi = \frac{d}{dt} \phi \quad (27)$$

where the overline is a weighted average over the states belonging to the given recurrent strongly connected component. The connection with the previous procedure involving the multiplication by vector of the left eigenspace can be seen by considering that  $(v_T, v_R) \tilde{M} = 0$  corresponds to requiring that  $v_R$  is in the left eigenspace of  $M_{R \rightarrow R}$  which is composed of block of unit vectors and that  $v_T = -v_R M_{T \rightarrow R} (M_{T \rightarrow T})^{-1}$ .

*Summary.* We presented a systematic method to derive an effective Markovian evolution on the slow scales involving fewer states. The extent of the simplification depends on the structure of the graph of fast transitions. If this graph is reducible it is possible to decrease the complexity of the initial problem. The key ingredients are the strongly connected components of the fast graph that identify the building blocks of the network. Only the components conserving probability on the fast scales (sinks of the graph condensation) will appear in the effective dynamics. Grouping the states into the strongly connected components is called averaging, whereas the elimination of the blocks that are not sinks is called decimation.

## 2.2. Block-diagonal fast dynamics

*Question.* How does the effective process look like when fast transitions have a block-diagonal structure?

When the fast transitions generator  $M$  can be cast in a block-diagonal form (see figure 5):

$$K = \begin{bmatrix} F_{i_\beta}^{i_\alpha} & S_{j_\beta}^{i_\alpha} & \dots & \dots \\ S_{i_\alpha}^{j_\beta} & F_{j_\beta}^{j_\alpha} & \dots & \dots \\ \vdots & \vdots & \ddots & \vdots \\ \dots & \dots & \dots & F_{k_\beta}^{k_\alpha} \end{bmatrix}.$$

all the identified blocks will conserve probability within them and will be part of the effective dynamics. In other words, no state will be eliminated. Such case has been studied in detail in a number of publications (see e.g. [14, 22, 41, 42, 17, 43, 6, 31]). It is convenient to label the states of the system highlighting the block-structure. We chose to identify a state as  $i_\alpha$  where the Latin letter  $i = 1 \dots n$  refers to the block and the Greek subscript  $\alpha = 1 \dots n_i$  denotes the specific state within the block. The asymptotic technique presented in the previous section will now provide the

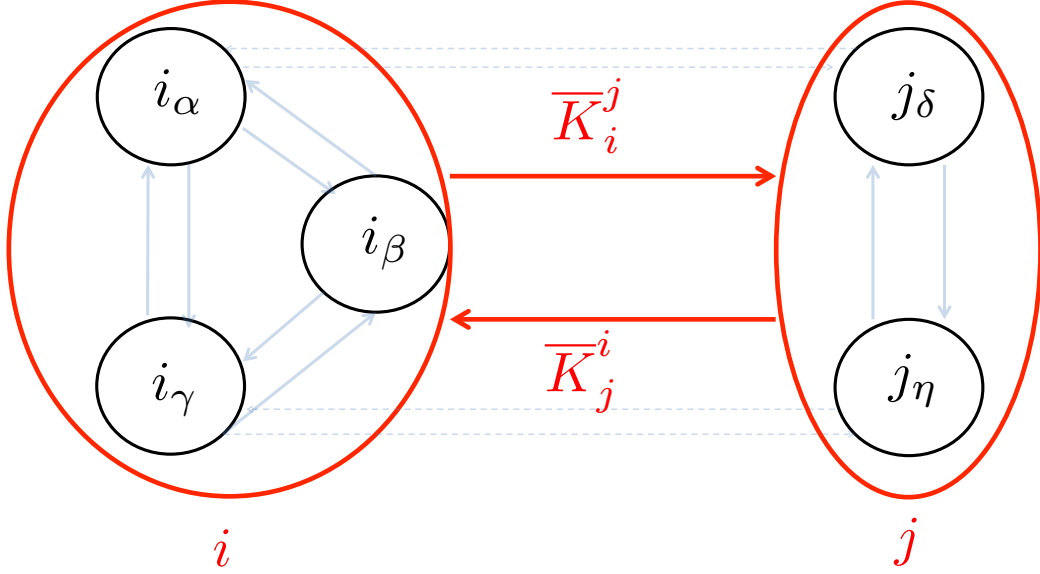


Figure 5: Example of a system with block-diagonal fast transitions. It is possible to identify blocks of states that are connected via fast transitions among themselves (solid lines) and by slow ones (dashed lines) to other blocks. The blocks are highlighted in red and the red arrows represent the effective transition across blocks as derived in eq. (29).

effective dynamics that connects the  $n$  slow blocks labeled by the Latin indices. A major simplification introduced by the block-diagonal structure is that, since each block conserves probability, the left nullspace has a simple structure. The number of blocks  $n$  sets its dimension and the space is spanned by  $n$  row vectors composed of ones in the states belonging to a given block and zeros elsewhere. Denoting the dimension of block  $i$  as  $n_i$ , the left nullspace is generated by

$$\hat{\phi}_{block} = \hat{\phi}_1(\underbrace{1, \dots, 1}_{n_1}, \underbrace{0, \dots, 0}_{\sum_{i=2}^n n_i}) + \hat{\phi}_2(\underbrace{0, \dots, 0}_{n_1}, \underbrace{1, \dots, 1}_{n_2}, \underbrace{0, \dots, 0}_{\sum_{i=3}^n n_i}) + \dots + \hat{\phi}_n(\underbrace{0, \dots, 0}_{\sum_{i=1}^{n-1} n_i}, \underbrace{1, \dots, 1}_{n_n}). \quad (28)$$

The most relevant consequence is that the product  $(\hat{p}^{(0)} L^{(0)} p^{(0)})_{block}$  in eq. (18) now results in the generator of the effective dynamics between blocks  $(L^{(0)}_{eff})_{block}$  being a weighted average of the transitions between blocks (as derived by e.g. [30, 14, 22]). More precisely, the effective transition rates are given by

$$(K_{eff})_j^i = \bar{K}_j^i = \sum_{\alpha, \beta} S_{j\beta}^{i\alpha} w_{j\beta} \quad (29)$$

where we recall that  $w_{j\beta}$  is the equilibrium probability of state  $j_\beta$  under the fast dynamics of  $M$  conditional on being in block  $j$  and  $S_{j\beta}^{i\alpha}$  is a slow transition from state  $j_\beta$  in block  $j$  to state  $i_\alpha$  in block  $i$ .

*Summary.* A block-diagonal structure of the fast transition allows for an immediate identification of the relevant states for the slow dynamics after averaging — these are the blocks themselves. None of the blocks will be decimated.

### 2.3. Examples of effective dynamics for discrete Markov chains

#### 2.3.1. Decimation: bursty protein production

Consider a toy model of protein production from a constitutively active gene. Protein synthesis involves two steps: transcription of the gene into a messenger RNA (mRNA) and translation of the mRNA into the protein. When the gene and the mRNA molecules are present only in a few copies, a stochastic treatment of the process is mandatory. Determining the dynamics and the fluctuations of the proteins is key to investigate cell to cell variability and the reliability of cellular processes [26, 44, 27]. When mRNA translation (protein production) and mRNA decay are faster than protein degradation and gene transcription it is possible to eliminate the mRNA states from the dynamics and obtain an effective equation for the protein dynamics which accounts for the fluctuations of the transient mRNA state [36, 39]. The general method presented in this section can be adapted to such system and gives the same elimination. The system states (identified by the number of proteins and mRNA molecules) and transitions are illustrated in fig. 6 and obey the following master equation:

$$\begin{aligned} \frac{d p(n, m)}{dt} = & c_0 p(n, m-1) + \epsilon^{-1} c_1 m p(m, n-1) + \epsilon^{-1} d_0 (m+1) p(n, m+1) + d_1 (n+1) p(n+1, m) \\ & - (c_0 + c_1 m + d_0 m + d_1 n) p(n, m) \end{aligned} \quad (30)$$

where  $m$  and  $n$  refer respectively to the number of mRNA molecules and proteins,  $c_0$  and  $\epsilon^{-1} d_0$  are the rate of mRNA synthesis and degradation and,  $\epsilon^{-1} c_1$  and  $d_1$  the ones of protein production and decay. As the number of states is

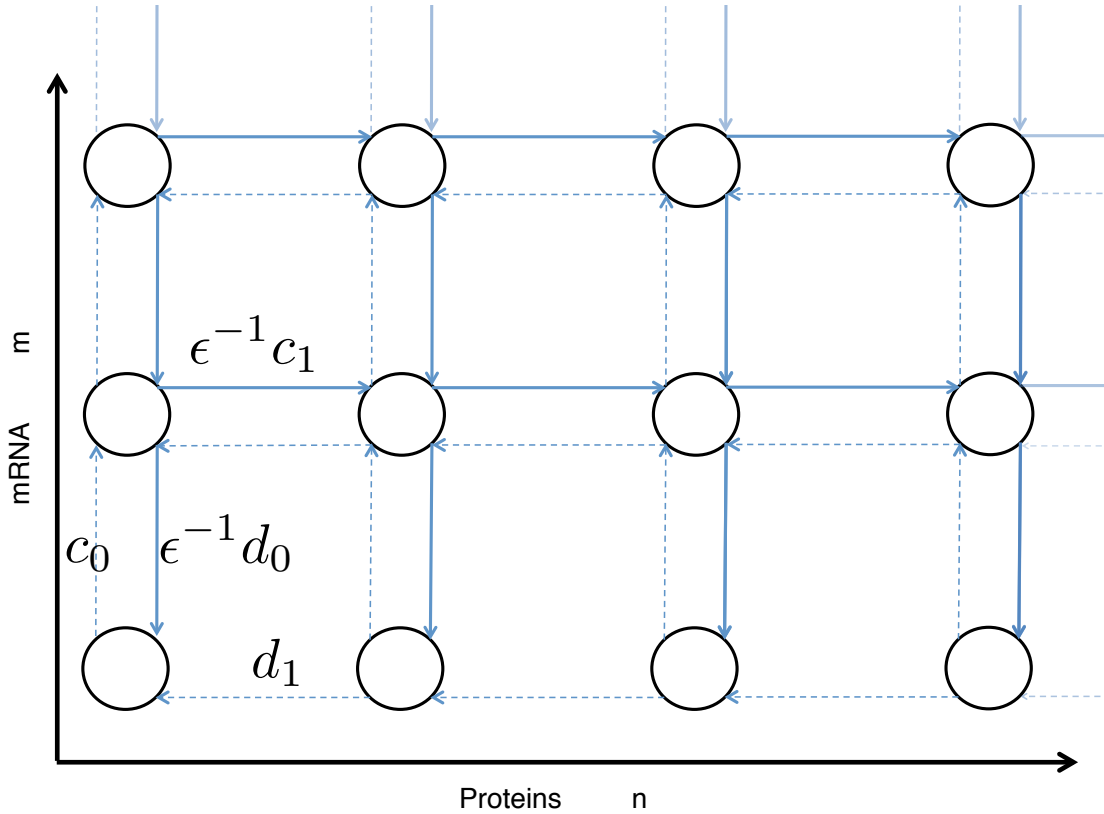


Figure 6: Schematic view of the Markov chain representing protein production and mRNA synthesis according to eq. 30.

unlimited it can become rather cumbersome to handle the probability vectors and transition matrix directly. However, by a suitable rearrangement of terms it is possible to identify blocks and reduce the system complexity. One needs to order states by grouping them according to the number of mRNA molecules  $\dots, \underbrace{(n=0, m=M), (n=1, m=M), \dots}_{m=M}$

$\underbrace{(n=0, m=1), (n=1, m=1), \dots}_{m=1}, \underbrace{(n=0, m=0), (n=1, m=0), \dots}_{m=0}$ . The corresponding matrix of fast transitions is

then already in the block triangular form with blocks of dimension 1 (made of single states). The only blocks conserving probability are the ones not having fast transitions outwards: *i.e.*, the ones having no mRNA molecules. All the states with  $m > 0$  will not conserve probability on the fast scale and will be decimated from the effective dynamics. For the sake of clarity we shall consider the case with at most one mRNA molecule (the general case of infinitely many mRNA yields the same effective dynamics<sup>3</sup>). The matrix of fast transition reads:

$$M = \left( \begin{array}{c|c} M_a & 0 \\ \hline M_b & 0 \end{array} \right) \quad (31)$$

where 0 represents a matrix with all entries equal to zero.  $M_a$  refers to fast transitions between states with one mRNA molecule ( $m = 1$ ) occurring with rate  $c_1$  and the exit rate from states with  $m = 1$ :  $(d_0 + c_1)$ . It is a band diagonal matrix with elements<sup>4</sup>  $M_a^{ij} = -(d_0 + c_1)\delta^{i,j} + c_1\delta^{i,j+1}$ . The fast transitions from states with  $m = 1$  to ones with  $m = 0$  are included in  $M_b$  which is a diagonal matrix with entries equal to  $d_0$ . The steady state probability for these states will be given by  $p^{(0)} = \sum_{i=0}^{\infty} \phi_i w^i$  where

$$w^i = \begin{pmatrix} w^{i_1} \\ w^{i_2} \end{pmatrix} \quad (32)$$

with  $w^{i_1}$  being a column vector with entries equal to zero for every  $i$  and  $w_k^{i_2} = \delta_{k,i}$  a column vector with one non-zero entry in position  $i$ :

$$p^{(0)} = \phi_0 \begin{pmatrix} 0 \\ \vdots \\ 0 \\ \hline 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} + \phi_1 \begin{pmatrix} 0 \\ \vdots \\ 0 \\ \hline 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} + \phi_2 \begin{pmatrix} 0 \\ \vdots \\ 0 \\ \hline 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} + \dots \quad (33)$$

where the upper block refers to states with  $m = 1$  and the lower one to those with  $m = 0$  and  $\phi_i$  denotes the probability of having  $i$  proteins. The left nullspace of  $M$  is spanned by  $\hat{p}^{(0)} = \sum_{i=0}^{\infty} \hat{\phi}_i v^i$  where  $v^i = (v^{i_1}, v^{i_2})$  with  $v^{i_1}$  being a row vector with entries  $k$

$$v_k^{i_1} = \begin{cases} q_+^{i-k} q_s & k \leq i \\ 0 & k > i \end{cases} \quad (34)$$

where  $q_+ = \frac{c_1}{d_0+c_1}$  is the probability that the next transition from a mRNA is translation into a protein and  $q_s = \frac{d_0}{d_0+c_1}$  that of mRNA decay.  $v^{i_2} = w^{i_2 T}$  ensures biorthonormality. We then have

$$\begin{aligned} \hat{p}^{(0)} &= \hat{\phi}_0 \left( \underbrace{q_s, 0, 0, \dots, 0}_{m=1} \middle| \underbrace{1, 0, 0, \dots, 0}_{m=0} \right) + \hat{\phi}_1 \left( \underbrace{q_s q_+, q_s, 0, \dots, 0}_{m=1} \middle| \underbrace{0, 1, 0, \dots, 0}_{m=0} \right) \\ &+ \hat{\phi}_2 \left( \underbrace{q_s q_+^2, q_s q_+, q_s, \dots, 0}_{m=1} \middle| \underbrace{0, 0, 1, \dots, 0}_{m=0} \right) + \dots \end{aligned} \quad (35)$$

<sup>3</sup>This follows from the fact that the only states which will not be decimated (the non vanishing entries of  $\phi^{(0)}$ ) are all in the block  $m = 0$  and that the only slow transitions from states with  $m = 0$  go to states with  $m = 1$  implying that  $L^{(0)} p^{(0)}$  from eq. (18) will not have any contributions from the states with  $m > 1$ .

<sup>4</sup>Since the lowest number of proteins is 0, for ease of notation, in this example we let the indices referring to proteins start at 0.

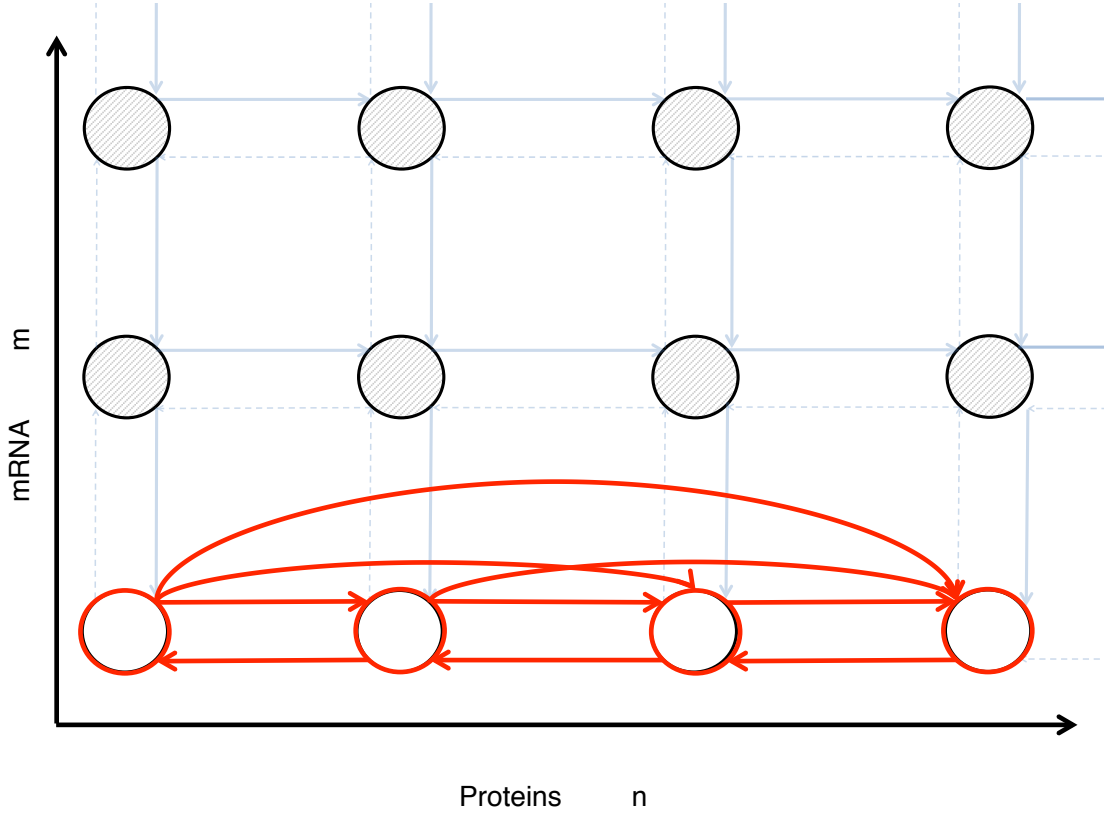


Figure 7: Effective dynamics representing protein production and mRNA synthesis according to eq. (38). The states having a non zero number of mRNA (shaded circles) have been decimated. The effective transitions (red arrows) now connect states that were not originally linked by single transitions.

The matrix of the slow transitions can be written as:

$$\mathbf{L}^{(0)} = \left( \begin{array}{c|c} \mathbf{L}_a^{(0)} & \mathbf{L}_c^{(0)} \\ \hline 0 & \mathbf{L}_a^{(0)} \end{array} \right) \quad (36)$$

where  $\mathbf{L}_a^{(0)}$  represents the slow transitions that do not change the number of mRNA (protein degradation with rate  $nd_1$ ) and the exit rates  $c_0 + nd_1$ . It is a band diagonal matrix with entries  $\mathbf{L}_a^{(0)ij} = -(c_0 + id_1)\delta^{i,j} + (i+1)d_1\delta^{i+1,j}$ .  $\mathbf{L}_c^{(0)}$  instead, accounts for the transitions changing the number of mRNA (RNA synthesis) and is a diagonal matrix with all entries equal to  $c_0$ . To derive the effective equation, following eq. (18), we need to evaluate

$$\mathbf{L}^{(0)} p^{(0)} = \left( \begin{array}{c} \mathbf{L}_c^{(0)} p_b^{(0)} \\ \mathbf{L}_a^{(0)} p_b^{(0)} \end{array} \right). \quad (37)$$

The effective evolution of the surviving state  $i$  is then obtained by multiplying by  $v^i$  and gives (as depicted in fig. 7):

$$\frac{d\phi_i}{dt} = c_0 q_s \sum_{l=0}^i q_+^l \phi_{i-l} + (i+1)d_1 \phi_{i+1} - (c_0 + id_1) \phi_i \quad (38)$$

which, modulo a time rescaling, is the result found in [36] expressed in their equation (14). The decimation procedure allowed to decrease the number of states in the effective dynamics, restricting it to the number of proteins modeled. At the same time, new connections between the surviving states appeared. Jumps in protein numbers no



longer need to be to the nearest state but can be larger, reflecting bursty protein synthesis. This biologically observed phenomenon simply results from the fact that several proteins can be produced during the short lifetime of a single mRNA molecule.

*Summary.* For slow proteins degradation and slow mRNA transcription, the bursty kinetics of protein synthesis from a constitutive active gene can be derived by decimation of the intermediate states involving mRNA translation and degradation.

### 2.3.2. Block diagonal: Two-component systems

To illustrate an application to the case of block-diagonal fast transitions let us consider the example of a simple biochemical network mimicking the sensing process of a cell [45]. The system is an extension of the one introduced in [46] which was further studied in [47]. We consider the sensing mechanisms to consist of a single receptor<sup>5</sup> that undergoes binding and unbinding with an external ligand at concentration  $c$ . We assume that a receptor bound to a ligand is in the active form and that an unbound one is not. The receptor, according to its activation state, acts on some downstream cytoplasmic proteins. We model this pathway by considering  $N$  proteins which can be phosphorylated or dephosphorylated with rates that depend on the activation state of the receptor as shown in figure 8. The activation dynamics of the receptor is influenced by the concentration of the external ligand and it is independent of the phosphorylation state of the proteins. Denoting the receptor as  $Y$  and the ligand concentration as  $c$  its dynamics follows



where in this reaction and the following ones appear the specific probability rate constants. The number of active (bound) receptors  $\bar{Y}$  is  $y = 0, 1$ . The receptor can reversibly activate (e.g. phosphorylate) the proteins



The number of phosphorylated proteins is  $x = 0, \dots, N$ . We do not consider spontaneous (non-mediated by the receptor) activation and deactivation. The phosphorylation reactions mediated by the active receptor are accompanied by ATP hydrolysis. We describe this system as a Markov chain in which a state is defined by the number of phosphorylated proteins and the corresponding activation state of the receptor as shown in figure 8. We consider the case in which the binding and unbinding of the receptor is much faster than the phosphorylation dynamics of the cytoplasmic proteins. This time-scale separation is observed, for instance, in bacterial chemoreceptors. To make explicit such scaling we write

$$ck_b \rightarrow \epsilon^{-1}ck_b \quad k_u \rightarrow \epsilon^{-1}k_u .$$

We can then write the master equation for the probability of being in the state  $y, x$  as

$$\frac{dp(y=0, x)}{dt} = \epsilon^{-1}k_u p(y=1, x) + (x+1)k_d p(y=0, x+1) + (N-x+1)k_p p(y=0, x-1) \quad (42)$$

$$\begin{aligned} & - \left[ xk_d + (N-x)k_p + \epsilon^{-1}ck_b \right] p(y=0, x) \\ \frac{dp(y=1, x)}{dt} & = \epsilon^{-1}ck_b p(y=0, x) + (x+1)k_d^* p(y=1, x+1) + (N-x+1)k_p^* p(y=1, x-1) \quad (43) \\ & - \left[ xk_d^* + (N-x)k_p^* + \epsilon^{-1}k_u \right] p(y=1, x) . \end{aligned}$$

Notice that actual transition rates increase with the total number of proteins so that care must be taken when considering large numbers of proteins. We here restrict to the case in which  $N \ll \epsilon^{-1}$ . Even for this simple system featuring

<sup>5</sup>The extension to an arbitrary number of receptors is straightforward

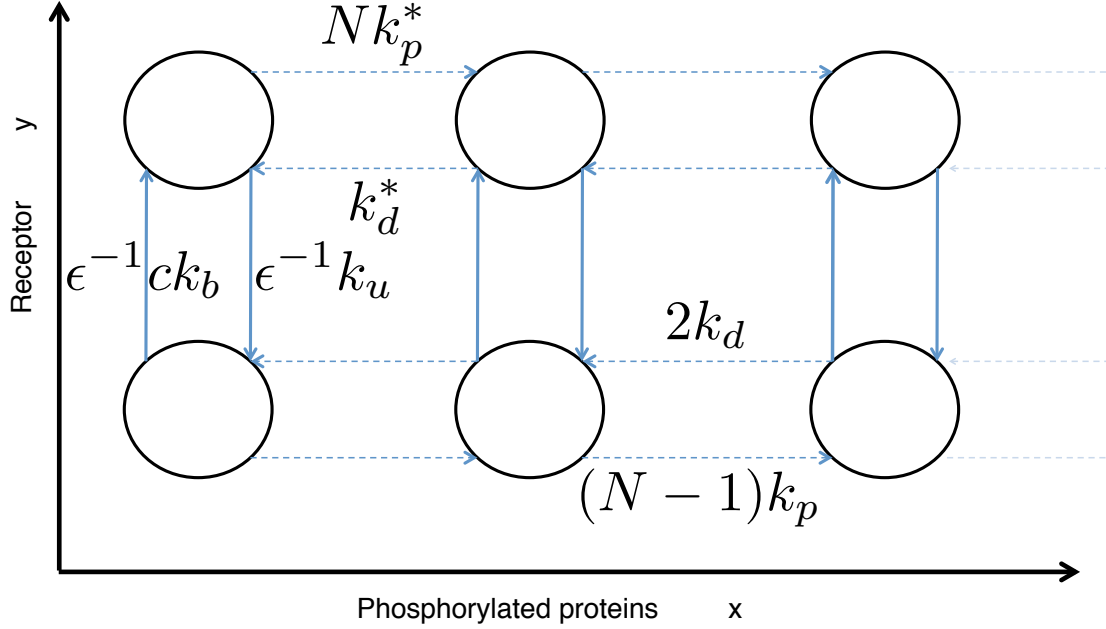


Figure 8: Schematic view of two chemical reactions implementing a sensing device as described in eq. (42). The variable  $y$  refers to the activity state of the receptor. The phosphorylated proteins are labeled by  $x$  and can take values from 0 to the total number of available proteins  $N$ . Each state is defined by the activity state of the receptor and the number phosphorylated proteins, i.e. the pair  $(x, y)$ . Vertical transitions correspond to receptors activation and deactivation and occur, respectively, with rates  $\epsilon^{-1}ck_b$  and  $\epsilon^{-1}k_u$ . The (de-)phosphorylation reactions result in horizontal transitions.

only two chemical reactions it is non-trivial to find an analytic solution of the steady state probability distribution (the authors of [46] derived it for an infinite pool of proteins). By ordering states as  $\dots, (n, y = 0), (n, y = 1); (n', y = 0), (n', y = 1); \dots$  the fast transitions, involving the receptor, are arranged in a block-diagonal manner. As shown in the general section, this simplifies the elimination procedure. At order  $\epsilon^{-1}$  the equation features only the receptor transitions and, after an initial transient relaxes to

$$p(y = 1) = p(ON) = \frac{ck_b}{k_u + ck_b} \quad p(y = 0) = p(OFF) = 1 - P(ON) = \frac{k_u}{k_u + ck_b} \quad (44)$$

where  $p(ON)$  is the probability of the receptor being active. The first order solution then reads:

$$p^{(0)} = \phi_0 \begin{pmatrix} p(OFF) \\ p(ON) \\ 0 \\ 0 \\ 0 \\ \vdots \end{pmatrix} + \phi_1 \begin{pmatrix} 0 \\ 0 \\ p(OFF) \\ p(ON) \\ 0 \\ \vdots \end{pmatrix} + \dots \quad (45)$$

where  $\phi_i$  denotes the first order probability of having  $i$  proteins phosphorylated. Given the block-diagonal structure of

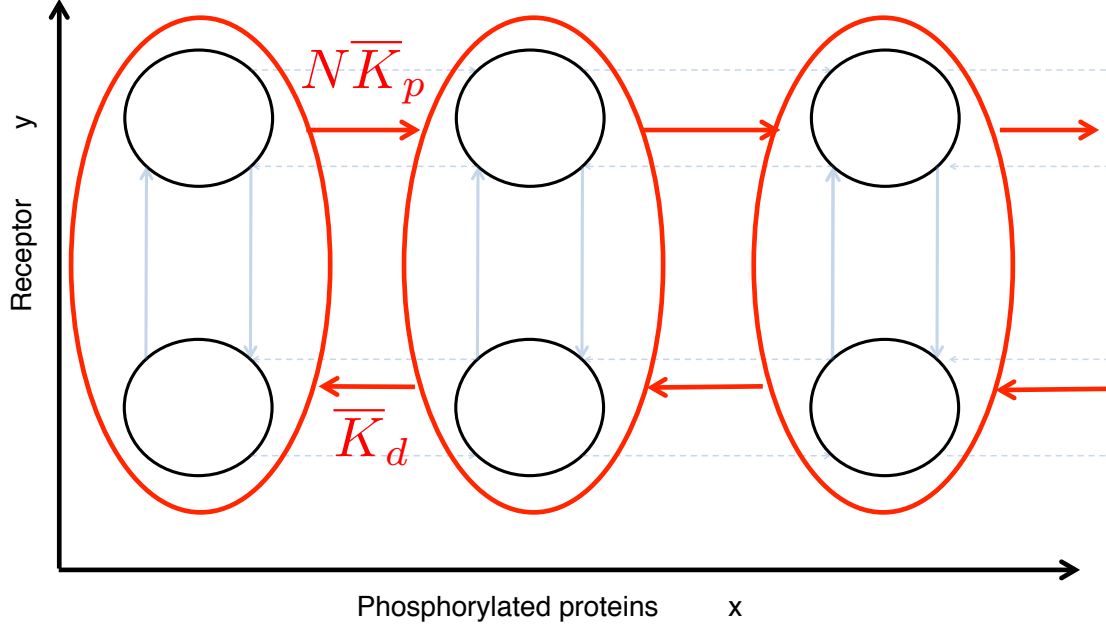


Figure 9: Effective dynamics after the averaging over receptor states as described in eq. (47).

the fast operator, its left nullspace is spanned by:

$$\hat{p}^{(0)} = \hat{\phi}_0 (1, 1, 0, 0, 0, \dots, 0) + \hat{\phi}_1 (0, 0, 1, 1, 0, \dots, 0) + \dots \quad (46)$$

so that we have the following effective equation for the protein dynamics

$$\frac{d\phi_x}{dt} = (x+1)(K_{eff})_d \phi_{x+1} + (N-x+1)(K_{eff})_p \phi_{x-1} - \left( x(K_{eff})_d + (N-x)(K_{eff})_p \right) \phi_x \quad (47)$$

where the effective rates are averages over the equilibrium distribution of receptor states:

$$(K_{eff})_p = \bar{K}_p = p(ON)k_p^* + p(OFF)k_p = \frac{ck_b k_p^* + k_u k_p}{k_u + ck_b} \quad (48)$$

and

$$(K_{eff})_d = \bar{K}_d = p(ON)k_d^* + p(OFF)k_d. \quad (49)$$

As shown in figure 9, after the averaging of the receptor states, the network has become one dimensional and the steady state solution of equation (47) can be easily found to be the binomial distribution

$$\phi_x^{ss} = a^x b^{N-x} \binom{N}{x} \quad (50)$$

where

$$a = \frac{(K_{eff})_p}{(K_{eff})_p + (K_{eff})_d} \quad b = \frac{(K_{eff})_d}{(K_{eff})_p + (K_{eff})_d}. \quad (51)$$

Exploiting the time-scale separation by means of the asymptotic techniques presented in the previous section we have managed to derive the steady state distribution of the system up to corrections of order  $\epsilon$ . We note that a very similar Markov network to the one we have considered (with different interpretation of the reactions giving rise to the transition rates) can be used to model receptor methylation as done by the authors of [41]. Under analogous time-scale separation assumptions they were able to derive solvable effective dynamics. In closing we remark that the same procedure could have been applied to a system with  $R$  independent receptors obeying

$$\begin{aligned} \frac{dp(y, x)}{dt} = & \epsilon^{-1}(y+1)k_u p(y+1, x) + \epsilon^{-1}(R-y+1)ck_b p(y-1, x) + \\ & (x+1)(yk_d^* + (R-y)k_d) p(y, x+1) + (N-x+1)(yk_p^* + (R-y)k_p) p(y, x-1) + \\ & - \left[ x(yk_d^* + (R-y)k_d) + (N-x)(yk_p^* + (R-y)k_p) + \epsilon^{-1}yk_u + \epsilon^{-1}(R-y)ck_b \right] p(y, x) \end{aligned} \quad (52)$$

and would have given similar results with the equilibrium distribution of the receptors being a binomial and with effective rates:

$$(K_{eff})_p^R = \langle y \rangle k_p^* + (R - \langle y \rangle) k_p = R \left( p(ON)k_p^* + p(OFF)k_p \right) \quad (K_{eff})_d^R = R \left( p(ON)k_d^* + p(OFF)k_d \right). \quad (53)$$

*Summary.* A two-component system where the receptor states evolve rapidly admits a block-diagonal structure. Averaging over the receptor states gives an effective Markovian kinetics between blocks identified by the number of phosphorylated proteins.

### 2.3.3. Stochastic Michaelis-Menten.

Let us consider the enzymatic reaction



converting a substrate  $S$  into a product  $P$  with the help of a catalytic enzyme  $E$ , via the intermediate state involving the complex  $C$ . For macroscopic chemical kinetics, various approximations lead to a simplified model known as Michaelis-Menten kinetics describing a hyperbolic dependence of the rate of product formation on the substrate concentration  $c_s$  (see e.g. [48]):

$$\frac{dc_p}{dt} = V_{max} \frac{c_s}{K_M + c_s}$$

where  $c_p$  is the product concentration and  $K_M$  is the Michaelis constant. The specific expression of  $K_M$  depends on the approximation exploited. The two most common approximations are the *quasi-equilibrium* and the *quasi-steady-state*. When the number of enzymes involved is small, their fluctuations become relevant and it is important to adopt a stochastic description that will take the form depicted in fig. 10. Several authors have studied how the approximations affect the stochastic version of such enzymatic kinetics [5, 32, 33, 34, 35, 38]. Here we present how to investigate the issue within the general averaging and decimation procedure discussed in the general section. For the sake of simplicity we assume the substrate to be abundant with a fixed concentration  $c_s$  and we consider the stochastic dynamics of the number of complexes  $c$  and product molecules  $d$ . The general case of a fluctuating substrate is considered in appendix A. The master equation governing the probability of being in a state  $p(c, d)$  is:

$$\frac{d}{dt} p(c, d) = k_1 c_s p(c-1, d) + k_{-1}(c+1) p(c+1, d) + k_2(c+1) p(c+1, d-1) - (k_1 c_s + k_{-1}c + k_2c) p(c, d) \quad (55)$$

where the enzyme switches between the free state and the complex with rate  $c_s k_1$  and back with  $k_{-1}$ . Also when a product is formed (rate  $k_2$ ) the complex involved in the reaction is back to the free enzyme form. It is important to notice that, when the three rates are comparable in magnitude, it is not possible to simplify the original equations and obtain an effective Markovian description for the dynamics of product formation. One could define blocks of states identified by the same number of product molecules but the waiting time for transitions across blocks would not be

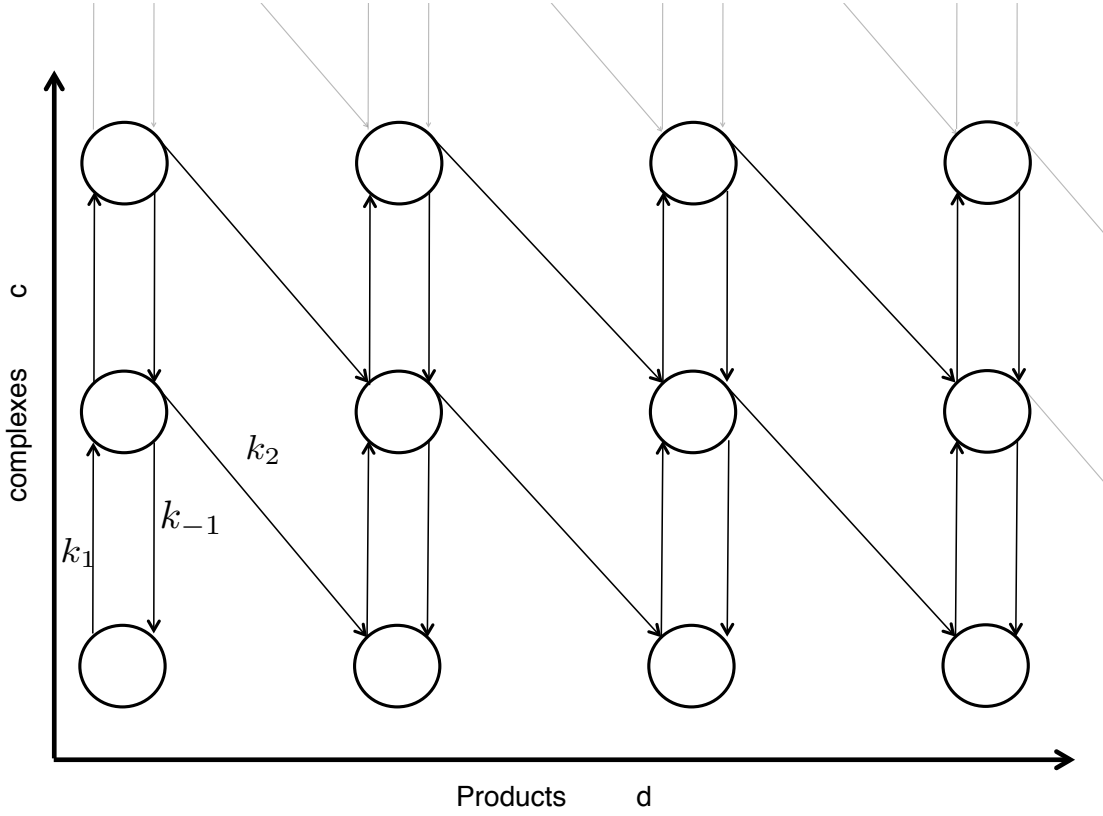


Figure 10: Schematic view of the Markov chain representing stochastic enzyme kinetics according to eq. 55.

distributed exponentially [35, 32, 33, 34, 38]. This occurs because the transitions between complex and free enzyme (within a block) take place with comparable rates to the one of product formation (across blocks). A systematic way of appreciating this point is to study the statistics of product formation by analyzing the moment generating function of the number of product synthesis events (as done for instance by [34, 38]). In the minimal case, one can consider the dynamics of a single enzyme, jumping to the complex state with a rate  $c_s k_1$  and returning to the free state either via unbinding from the substrate (rate  $k_{-1}$ ) or upon product formation (rate  $k_2$ ). The moment generating function of the number of product formation events  $n_2$  in a time  $t$  is:

$$G_2(s, t) = \sum_{n_2=0}^{\infty} p(n_2, t) e^{-s n_2}. \quad (56)$$

where  $p(n_2, t)$  is the probability of observing a number  $n_2$  of product syntheses in a time  $t$ . Such quantity obeys the equation

$$\frac{dG_2(s, t)}{dt} = M_s G_2(s, t) \quad (57)$$

with the deformed fast matrix

$$M_s = \begin{pmatrix} -c_s k_1 & k_2 e^{-s} + k_{-1} \\ c_s k_1 & -k_2 - k_{-1} \end{pmatrix}.$$

At long times, the evolution of the generating function is determined by the largest eigenvalues of the modified transition matrix:  $G_2(s, t) \sim e^{\lambda_+(s)t}$  with

$$\lambda_+(s) = \frac{-(c_s k_1 + k_2 + k_{-1}) + \sqrt{(c_s k_1 + k_2 + k_{-1})^2 - 4(1 - e^{-s})c_s k_1 k_2}}{2} \quad (58)$$

showing that the average rate of production reads:

$$-\frac{1}{t} \frac{\partial G_2(s, t)}{\partial s} \Big|_{s=0} = c_s k_1 k_2 / (c_s k_1 + k_2 + k_{-1}) . \quad (59)$$

This average is consistent with the Michaelis-Menten rate under the quasi-steady-state assumption. However, the other moments do not follow a Poissonian distribution, in general. Indeed, recalling that the moment generating function of a Poissonian variable obeys  $G_{Poisson}(s, t) = \exp(\mu(t)(e^{-s} - 1))$  we see that product formation can be approximately Poissonian if

$$c_s k_1 k_2 \ll (c_s k_1 + k_2 + k_{-1}) . \quad (60)$$

The same condition can be derived by studying the first passage time between neighbouring product states yielding eq. (34) in [33]. Other approximations relying on the large abundance of products are possible (see e.g. [5]) but they cannot be cast in terms of the systematic procedure presented here and they do not justify an exponential waiting time between individual transitions involving product states.

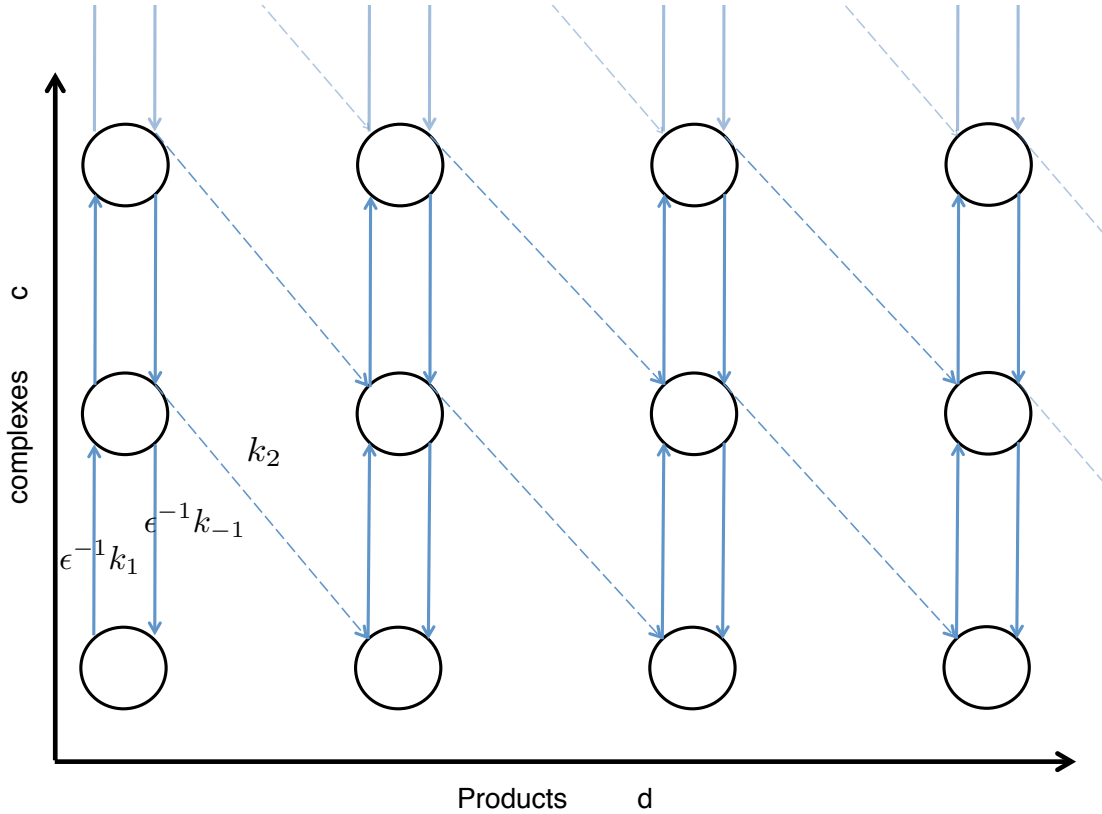


Figure 11: Quasi-equilibrium Michaelis-Menten.

*Quasi-equilibrium stochastic Michaelis-Menten.* The quasi-equilibrium approximation is valid when the dynamics of complex formation is much faster than product synthesis:  $c_s k_1, k_{-1} \gg k_2$ . Then, enzyme and complex reach an equilibrium between any product formation event. We make this scaling explicit by writing  $c_s k_1 \rightarrow \epsilon^{-1} c_s k_1$  and  $k_{-1} \rightarrow \epsilon^{-1} k_{-1}$ . By examining figure 11, it is possible to identify blocks of rapidly connected states. The blocks are characterized by the same number of products and different complexes. From eq. (60) we expect the transition between blocks to follow a Poisson process. Since the generator of the fast transitions can be cast in a block-diagonal way, the effective dynamics between different blocks (number of products) can be obtained as shown in section 2.2

(as also done in the previous example in section 2.3.2). The effective rate of product formation, once the complex state has been averaged out, will be, following eq. (29),

$$\overline{K_p} = \sum_{c=0}^{e_n} w_d(c) c k_2 = \langle c \rangle_d k_2 = e_n k_2 \frac{c_s}{k_{-1}/k_1 + c_s} \quad (61)$$

where  $e_n$  is the number of total enzymes available,  $w_d(c)$  is the first order approximation to the equilibrium probability of having  $c$  complexes when having  $d$  products and  $\langle c \rangle_d$  is its average. In this case, it does not depend on the number of present products  $d$  and is simply the binomial distribution:  $w_d(c) = B(e_n, \frac{c_s}{k_{-1}/k_1 + c_s})$ . We have then an effective dynamics between blocks as depicted in fig. 12. The expression in eq. (61) reproduces the result of the quasi-equilibrium approximation for macroscopic chemical kinetics which gives  $K_M^{eq} = k_{-1}/k_1$ .

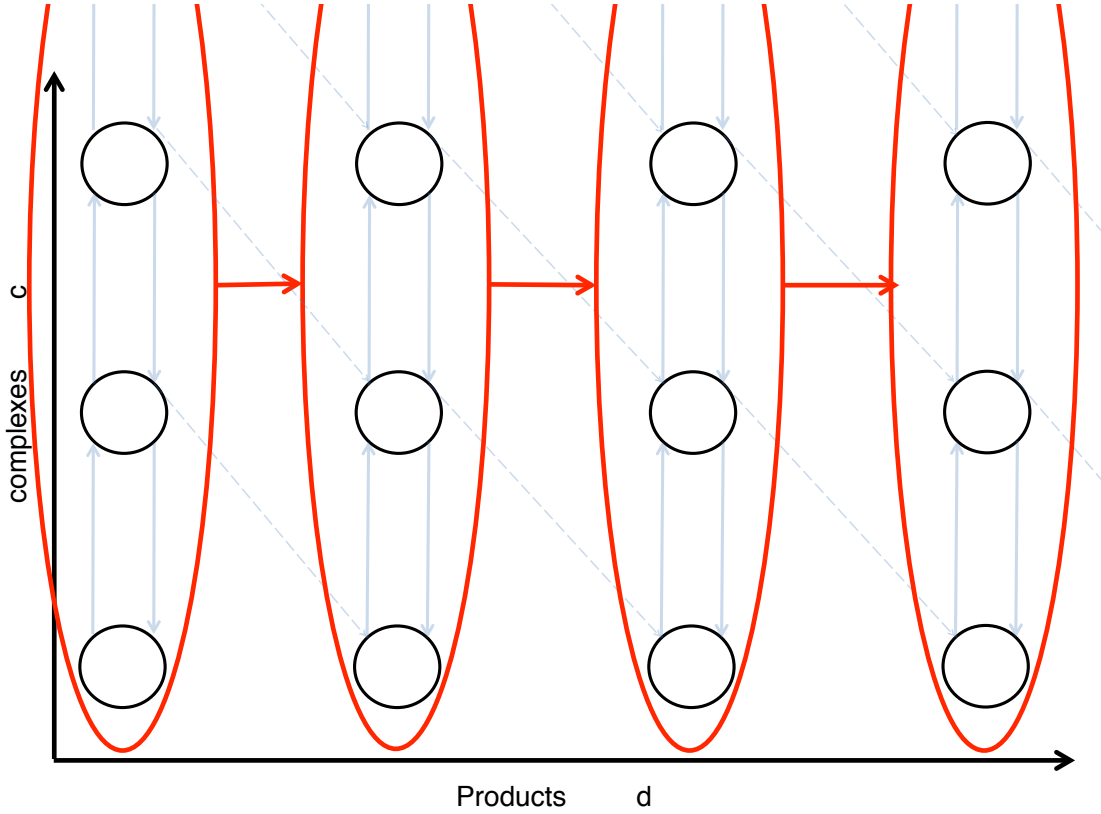


Figure 12: Effective dynamics for the quasi-equilibrium Michaelis-Menten.

*Quasi-steady-state stochastic Michaelis-Menten with slow complex formation.* As shown in eq. (60), when complex formation is slow compared to product synthesis and complex dissociation ( $c_s k_1 \ll k_{-1}, k_2$ , see fig. 13) the transitions between product states will approximately follow a Poisson process. At variance with the quasi-equilibrium case, we will obtain a Markovian dynamics between different product numbers not by averaging over complex states but by decimating the states with  $c > 0$  (as done, e.g., by the authors of [35]). Broadly speaking, the exponentially distributed exit times are recovered since complex formation is a rate limiting step, a rare event. With the general approach presented in this section we can obtain the effective rate of product formation when complex formation is slower than both complex degradation and product synthesis. Consider one total enzyme and order the states as  $\dots, (c = 1, d), (c = 1, d + 1), \dots, (c = 0, d), (c = 0, d + 1) \dots$  so that the fast transition matrix is block-triangular:

$$M = \begin{pmatrix} M_a & 0 \\ M_b & 0 \end{pmatrix} \quad (62)$$

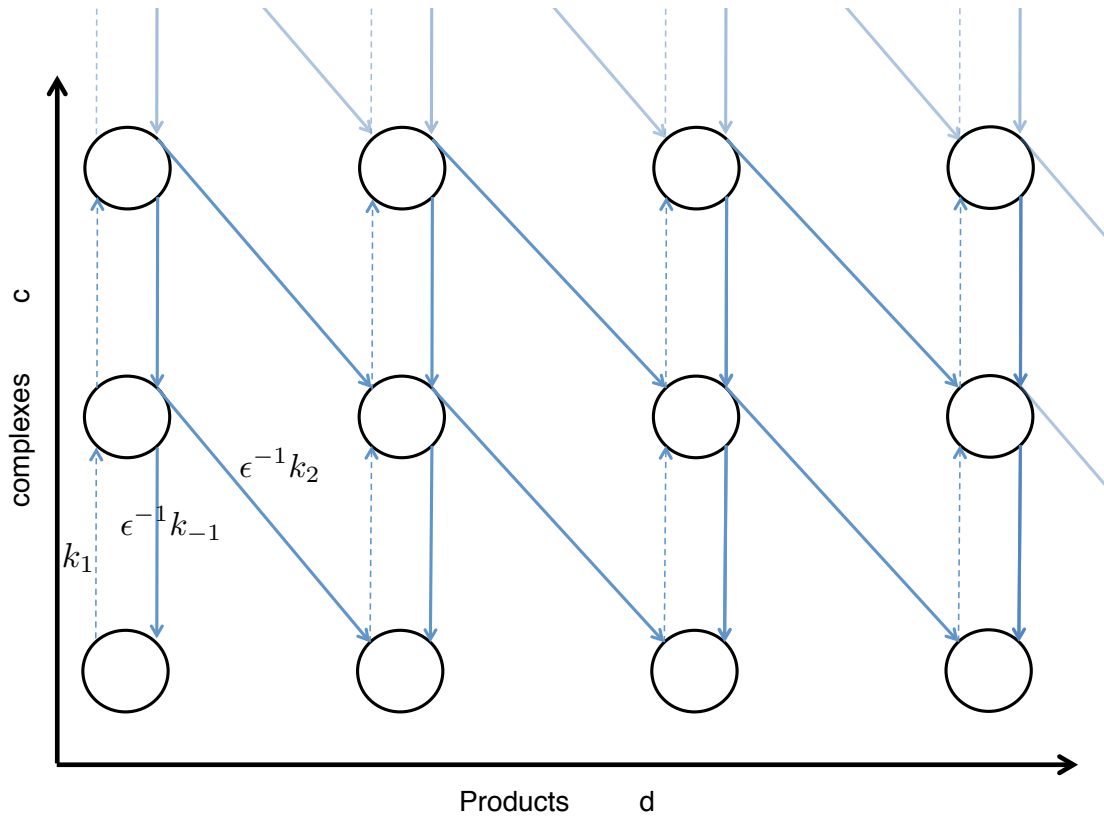


Figure 13: Quasi-steady state Michaelis-Menten with slow complex formation.

where 0 represents a matrix with all entries equal to zero.  $M_a$  contains the fast exit rate from the states with complex  $c = 1$  and it is a diagonal matrix with entries:  $-(k_{-1} + k_2)$ . The fast transitions from states with a complex ( $c = 1$ ) to ones with a free enzyme ( $c = 0$ ) are included in  $M_b$  which is a band diagonal matrix  $M_b^{ij} = k_{-1}\delta^{i,j} + k_2\delta^{i,j+1}$ . The states with  $c > 0$  do not conserve probability and can therefore be decimated. The probability relaxes on the fast scales to

$$p^{(0)} = \phi_0 \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} + \phi_1 \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} + \phi_2 \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} + \dots \quad (63)$$

where the upper block refers to states with  $c = 1$  and the lower one to those with  $c = 0$  and  $\phi_i$  denotes the first order approximation to the marginal probability of having  $i$  product molecules.



The left nullspace of  $M$  is spanned by

$$\begin{aligned} \hat{p}^{(0)} = & \hat{\phi}_0 \left( \underbrace{\frac{k_{-1}}{k_{-1} + k_2}, 0, 0, \dots, 0}_{c=1} \middle| \underbrace{1, 0, 0, \dots, 0}_{c=0} \right) + \hat{\phi}_1 \left( \underbrace{\frac{k_2}{k_{-1} + k_2}, \frac{k_{-1}}{k_{-1} + k_2}, 0, \dots, 0}_{c=1} \middle| \underbrace{0, 1, 0, \dots, 0}_{c=0} \right) \\ & + \hat{\phi}_2 \left( \underbrace{0, \frac{k_2}{k_{-1} + k_2}, \frac{k_{-1}}{k_{-1} + k_2}, 0, \dots, 0}_{c=1} \middle| \underbrace{0, 0, 1, \dots, 0}_{c=0} \right) + \dots \end{aligned} \quad (64)$$

The slow transition matrix reads:

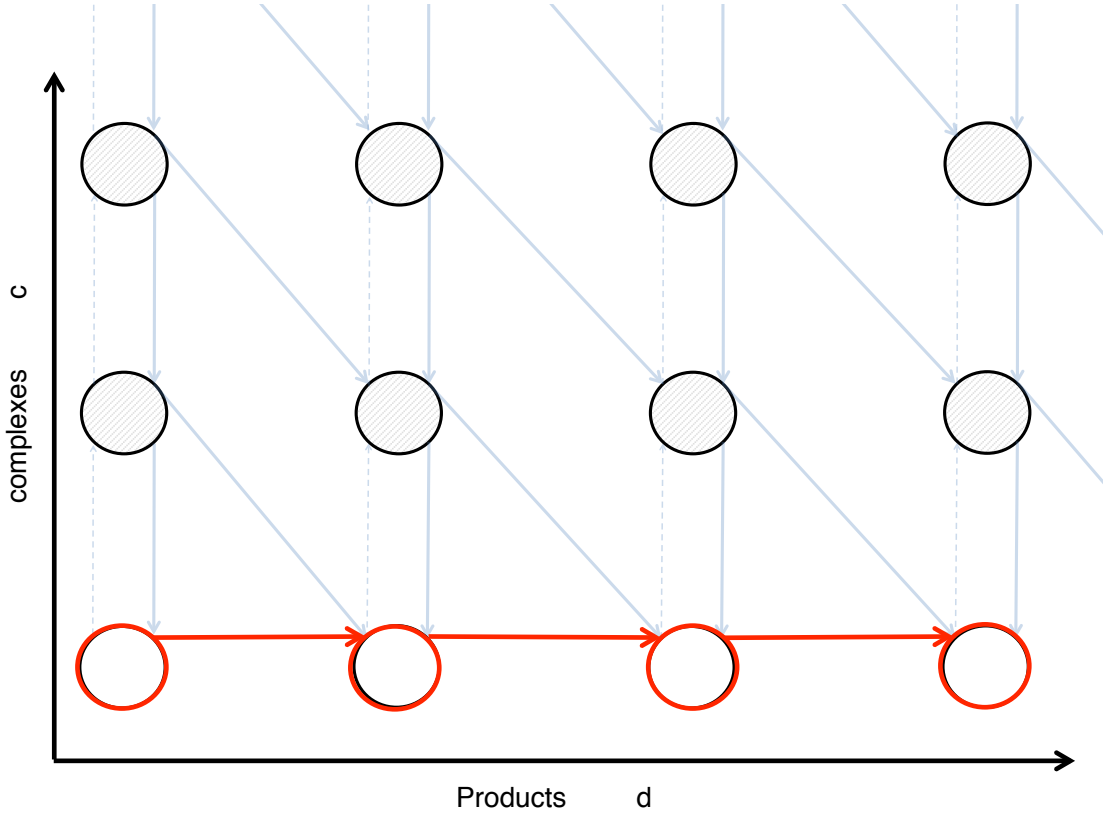


Figure 14: Effective quasi-steady state Michaelis Menten with slow complex formation.

$$L^{(0)} = \left( \begin{array}{c|c} 0 & L_c^{(0)} \\ \hline 0 & -L_c^{(0)} \end{array} \right) \quad (65)$$

with  $L_c^{(0)}$  being a diagonal matrix with entries  $c_s k_1$ . The effective equation is found to be

$$\frac{d\phi_0}{dt} = -k_2 \frac{c_s k_1}{k_{-1} + k_2} \phi_0 \quad (66)$$

$$\frac{d\phi_i}{dt} = \left( k_2 \frac{c_s k_1}{k_{-1} + k_2} \right) (\phi_{i-1} - \phi_i) \quad i > 0 \quad (67)$$

and takes place on the states with no complex ( $c = 0$ ) as depicted in fig. 14. The Michaelis constant for the quasi-steady-state approximation of macroscopic chemical kinetics is  $K_M^{qss} = \frac{k_{-1} + k_2}{k_1}$ . For small complex formation rates the

rate of product synthesis is

$$\frac{dc_p^{qss}}{dt} = k_2 \frac{c_s k_1}{k_{-1} + k_2 + c_s k_1} \simeq k_2 \frac{c_s k_1}{k_{-1} + k_2} \quad (68)$$

yielding an approximately linear dependence on the substrate. The stochastic transition rate derived with the decimation procedure coincides with such macroscopic rate.

*Summary.* The stochastic Michaelis-Menten kinetics can be simplified to give an effective kinetics for products only, under the assumptions that some rates are much larger than others. Specifically, the quasi-equilibrium approximation (fast substrate-enzyme binding and unbinding) has a block structure that through averaging gives the slow evolution in terms of the blocks with different numbers of product molecules. The case of slow binding of the substrate (but fast unbinding and product formation) is a sub-case of the quasi-steady-state approximation and via decimation gives an effective evolution between the states with no complexes (all enzymes unbound) and different number of products.

#### 2.3.4. The flagellar motor of *E. coli*

Let us now consider a case involving three different well separated time scales taken from the kinetics of *E. coli* flagellar motor [49]. The approach and results presented below are discussed in detail in Ref. [50].

The ring of proteins forming the motor of the *E. coli* flagella has been shown to be very well described by the conformational spread model [51, 52, 53, 54]. This model consists in  $N$  identical units, or protomers<sup>6</sup>, each of which can appear in two different states, active ( $A$ ) or inactive ( $I$ ): a protomer in the active state increases the probability of CW rotation of the motor, and of CCW rotation in the inactive state (see Fig. 15). Moreover, each protomer can also

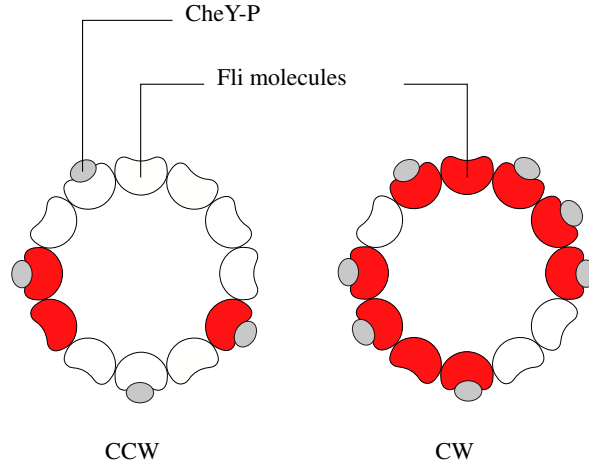


Figure 15: The flagellar motor. The protomers (Fli molecules) are represented in white (inactive state,  $I$ ) and red (active state,  $A$ ), while the CheY-P regulator is the grey spot. The motor rotates counterclockwise when most of the protomers are in the inactive state (left) and clockwise otherwise (right).

bind a ligand, corresponding to the CheY-P chemotactic regulator: we refer to the protomer as in the bound ( $B$ ) state when a ligand is attached to it, or unbound ( $U$ ) otherwise. Therefore, the single protomers can be in 4 different states, corresponding to all the possible activity and binding configurations.

The protomers are coupled via a nearest neighbour interaction, which depends on their activity states only: in particular, the energy is lowered by a quantity  $J$  when the neighbouring protomers are in the same activity state  $A$  or  $I$ .

<sup>6</sup>Not to be confused with promoters

Associating to each protomer a spin variable  $\sigma_i$  taking value  $+1$  when the protomer is active ( $\alpha_i = A$ ), or  $-1$  when it is inactive ( $\alpha_i = I$ ), one can represent the states of the system as  $s = \{(\sigma_i, \ell_i)\}_{i=1}^N$ . The kinetics of the conformational spread model is then governed by the master (Kolmogorov) equation

$$\frac{d}{dt}P(s, t) = \sum_{s'} [P(s', t) K(s' \rightarrow s) - P(s, t) K(s \rightarrow s')] \quad (69)$$

where the rates are

$$K(s \rightarrow s') = \left\{ \frac{\omega_f}{1-\gamma} \left( 1 - \gamma \sigma_i \frac{\sigma_{i+1} + \sigma_{i-1}}{2} \right) e^{\beta h(-\sigma_i, \ell_i)} \delta_{\sigma'_i, -\sigma_i} \delta_{\ell'_i, \ell_i} + \omega_s e^{\beta h(\sigma_i, 1-\ell_i)} \delta_{\sigma'_i, \sigma_i} \delta_{\ell'_i, 1-\ell_i} \right\} \prod_{j \neq i} \delta_{\sigma'_j, \sigma_j} \delta_{\ell'_j, \ell_j} \quad (70)$$

Each term between the curly brackets in Eq. (70) is obtained from detailed balance up to multiplicative factors  $\omega_f$  and  $\omega_s$ : these constants account for typical time scales of the flipping and binding process, respectively. The constant  $\gamma$  in the spin-flip contribution is set by the strength of the ferromagnetic coupling,  $\gamma = \tanh(\beta J)$ .

For a protomer in the activity state  $\alpha$  (either  $A$  or  $I$ ), the rates of binding and unbinding are respectively given by:

$$\omega_s c k_b^\alpha \quad \text{and} \quad \omega_s k_u^\alpha \quad (71)$$

The ratio between the rate constants  $k_u^\alpha/k_b^\alpha$  is the dissociation constant of the binding process,  $K_d^\alpha$ :

$$K_d^\alpha = \frac{k_u^\alpha}{k_b^\alpha} = c_0 e^{-\beta(\varepsilon_b^{(\alpha)} + \mu_0)} \quad (72)$$

We also define the constants  $k_a$  and  $k_i$  as

$$k_a = \omega_f e^{\beta \varepsilon_I} \quad \text{and} \quad k_i = \omega_f e^{\beta \varepsilon_A} \quad (73)$$

which are the rate constants for activation and inactivation of the single protomer with  $\ell = 0$ ; the rates in the case  $\ell = 1$  are chosen compatibly with detailed balance condition. The ratio  $k_i/k_a$  is called allosteric constant,  $L$ :

$$L = \frac{k_i}{k_a} = e^{\beta(\varepsilon_A - \varepsilon_I)} \quad (74)$$

It is worth noticing that the binding/unbinding rates at one protomer only depend on the state of the protomer itself and no other protomer in the ring: this assumption of independent binding is typical of allosteric models.

Experimental data provide evidence that the system has three well-separated time scales for the kinetics (see Fig. 16: fast coarsening of activity domains due to strong coupling  $\beta J \gg 1$ , slow nucleation and even slower binding/unbinding. These are summarized by the inequalities  $\omega_s \ll \omega_f \ll \omega_f/(1-\gamma)$ .

Following Ref.[50] we show below how the strong coupling limit amounts to reducing the conformational spread model to an effective Monod–Wyman–Changeux model [55] and the slow-binding limit further reduces it to an effective cooperative binding model.

#### *Decimation: from the Conformational Spread Model to MWC*

The fastest rates are

$$K_f^{(i)}(s \rightarrow s') = \frac{1}{N} \frac{\omega_f}{1-\gamma} \left( 1 + \sigma_i \frac{\sigma_{i+1} + \sigma_{i-1}}{2} \right) \delta_{\sigma'_i, -\sigma_i} \delta_{\ell'_i, \ell_i} \quad (75)$$

The coherent configurations with all spins equal are thus the only absorbing states of the process. The dynamics specified by  $K_f$  forbids the creation of pairs of domain walls, while it allows their annihilation. Fast transitions are allowed within sets of states characterized by the same number of domains, and towards states with fewer domains. As a result, the dynamics leads to one or the other coherent configuration (all protomers active or inactive) exponentially fast, with a typical rate  $\sim \omega_f/(1-\gamma)$ .

Therefore, on the typical time-scale of the switching dynamics, set by the rate  $\omega_f$ , the conformational spread model reduces to the MWC model with  $N$  binding sites and two global activity states. While transition rates from active to inactive states depend on the arrangement of bound ligands over the  $N$  sites, the equilibrium properties depend only on the total number of ligands bound. This property enables a further simplification when binding/unbinding is slower than switching.

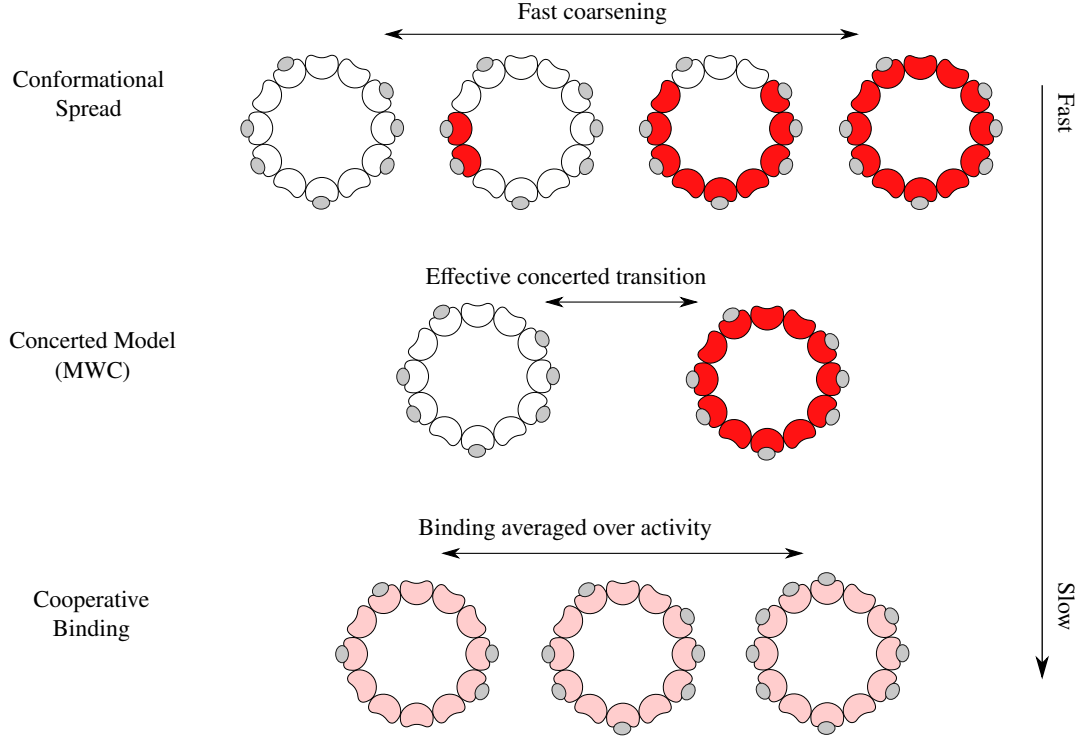


Figure 16: Time-scale separation in the Conformational Spread Model. Graphical representation of the time-scale separation scheme. Short-lived transient states containing domain walls are decimated in a first time-scale separation, leading from the Conformational Spread to the MWC model, while the binding dynamics is kept frozen. Then, over the binding time scales the activity states are averaged out, resulting into a cooperative binding model.

#### Averaging: from MWC to a cooperative binding model

For slow binding/unbinding, the activity of the ring rapidly relaxes to equilibrium at a given value of bound protomers  $l$ :

$$P_{eq}(I|l) = \frac{P_{eq}(l,I)}{P_{eq}(l)} = \frac{P_{eq}(l,I)}{P_{eq}(l,I) + P_{eq}(l,A)} = \frac{1}{1 + \frac{k_a}{k_i} \left( \frac{K_d^I}{K_d^A} \right)^l} \quad (76)$$

$$P_{eq}(A|l) = \frac{P_{eq}(l,A)}{P_{eq}(l)} = \frac{P_{eq}(l,A)}{P_{eq}(l,I) + P_{eq}(l,A)} = \frac{1}{1 + \frac{k_i}{k_a} \left( \frac{K_d^A}{K_d^I} \right)^l} \quad (77)$$

Then, on time scales comparable to or larger than  $\omega_s^{-1}$ , the relevant dynamics is essentially the slow binding/unbinding one, while the fast activation/inactivation dynamics is averaged over the equilibrium conditional probabilities in Eqs. (76)–(77), to give the effective rates  $\bar{K}$  for the variable  $l$ :

$$\bar{K}(l \rightarrow l') = \sum_{\alpha \in \{I,A\}} P_{eq}(\alpha|l) K(l \rightarrow l', \alpha \rightarrow \alpha) \quad (78)$$

Namely,

$$\bar{K}(l \rightarrow l+1) = (N-l) c \bar{k}_b^{(l)} \equiv b_l \bar{K}(l \rightarrow l-1) = l \bar{k}_u^{(l)} \equiv u_l \quad (79)$$

where

$$\bar{k}_{b,u}^{(l)} = \frac{k_{b,u}^A}{1 + \frac{k_i}{k_a} \left( \frac{K_d^A}{K_d^I} \right)^l} + \frac{k_{b,u}^I}{1 + \frac{k_a}{k_i} \left( \frac{K_d^I}{K_d^A} \right)^l}. \quad (80)$$

The process hence obtained is a birth-and-death process, restricted on the set of integers between  $l = 0$  and  $l = N$ . The resulting effective cooperative binding model reproduces well the experimental observations, see [50].

*Summary.* The flagellar motor of *E. coli* involves three widely separated timescales. By first decimating and then averaging it is possible to obtain an effective kinetics in terms of a cooperative binding model.

### 2.3.5. Random graphs

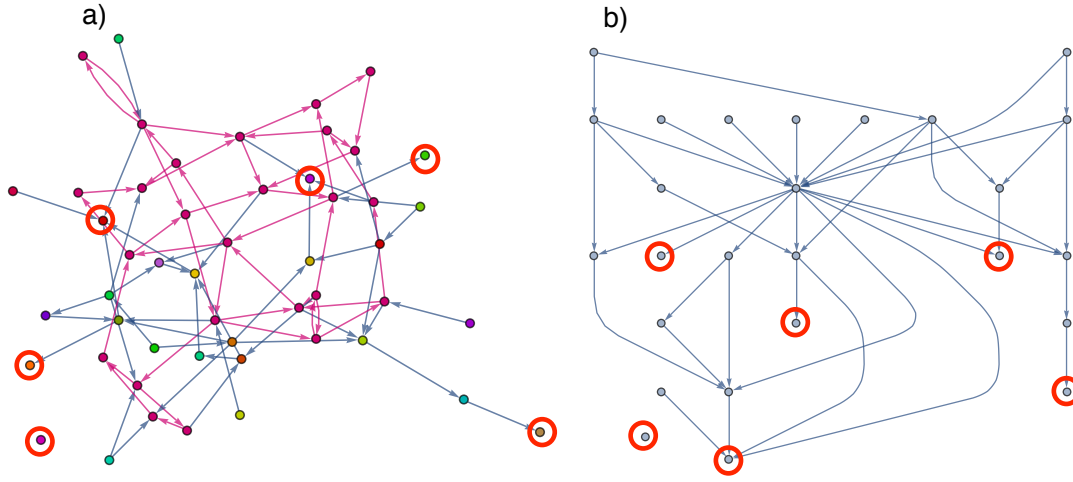


Figure 17: a) Network of the fast transitions between 50 states generated by drawing edges with probability  $p = c/(n-1)$  with  $c = 1.5$ . The network has one large strongly connected component involving 25 states (connected by purple arrows) and 25 states not strongly connected (each forming a strong component of size 1). b) The condensation of the network is the acyclic directed graph showing transitions between the components. From its analysis it is possible to identify the states that conserve probability that are the ones with no outgoing links: the "sinks". The red circles identify the strongly connected components that conserve probability: i.e., the ones that "survive" the decimation procedure.

The transitions networks discussed so far originated from chemical and biochemical systems and had regular structures. Let us now consider how the presented approach can be applied to more general (less structured) cases as, for instance, random directed graphs. Take a system with  $n$  states and, for the sake of simplicity, let us assume that the fast transition are given by a random Bernoulli directed graph  $\vec{D}(n, p)$  which is composed of  $n$  vertices and with directed edges randomly drawn independently with probability  $p$ . An example of a network with 50 states and an average outgoing (and incoming) edge number per state of 1.5 generated from  $\vec{D}(n = 50, p = 1.5/49)$  is given in figure 17. An alternative visualization is given by the adjacency matrix in figure 18. The procedure starts with the identification of the strongly connected components. For the case at hand there is one large component involving 25 states and 25 components made of a single state. The next step is to study the transitions across such components and identify the ones conserving probability. This can be done by studying the condensation of the graph and retaining only the sinks. Equivalently, one can cast the adjacency matrix in the block triangular form and keep only the blocks that conserve probability i.e. the ones that have no off-diagonal blocks. In this example there are only six

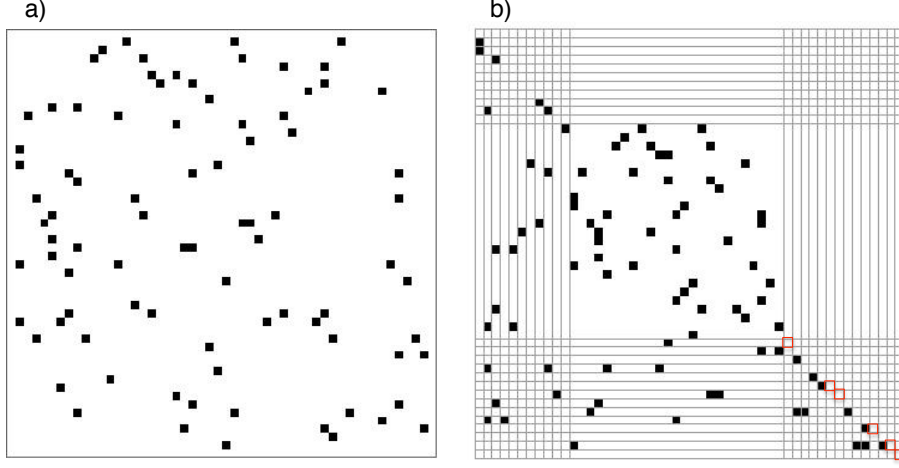


Figure 18: a) Adjacency matrix of the network of the fast transitions between 50 states generated by drawing edges with probability  $p = c/(n - 1)$  with  $c = 1.5$ . b) Rearrangement of the states to obtain a block triangular adjacency matrix. The large connected component is evident. The states in red are the ones conserving probability.

components conserving probability which means that the effective dynamics will take place on a much smaller set of states compared to the original dynamics. However, to obtain such effective dynamics, one needs to invert the matrix containing transitions between the 44 transient states. In general the extent to which the time scale-separation can reduce the complexity of the original dynamics depends on the structure of the fast transitions. The relevant features are the number of strongly connected components, their size and how many of them conserve probability. If few components conserve probability the effective dynamics will be simpler but its derivation will require the inversion of a larger matrix. For large random directed graphs a few results about the size of the largest strongly connected component and the number of strong components are known (see e.g. [56]). When  $c = p/n > 1$  the size of the largest strongly connected component is, with high probability, a finite fraction of the number of vertices. More precisely, the fraction is  $(1 - x/c)^2$  where  $x < 1$  is defined by  $xe^{-x} = ce^{-c}$ . The other strong components are logarithmic in size. For less connected graphs, when  $c < 1$ , all strong connected components are either cycles or single vertices. The number of nodes in each cycle is at most  $\omega$  for any  $\omega(N)$  such that  $\lim_{N \rightarrow \infty} \omega(N) = \infty$  no matter how slowly. To provide an intuition on how the relevant features of random direct graph depend on the connectivity we plot the average size of largest component, number of components and of sinks (components conserving probability) from a thousand random graphs in figure 19.

*Summary.* The problem of determining the relevant states on which the process effectively evolves on the slow time-scale can be cast in terms of the identification of the sinks of the graph condensation of the fast transitions. The method we have presented in the previous section applies to more complex network structures as well. Making use of established algorithms for deriving the condensation of a graph with linear complexity, one can efficiently identify which states of the original system will appear in the effective dynamics.

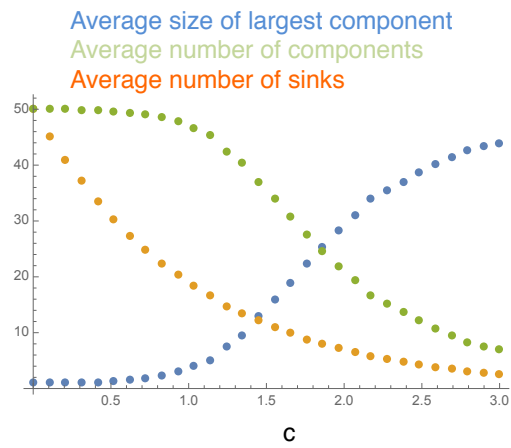


Figure 19: Decimation and averaging of a Markov chain on a graph with 50 nodes: average size of largest component, number of components and of sinks (components conserving probability) from a thousand random graphs in figure as a function of the parameter  $c$  which determines the probability of drawing an edge  $p = c/(n - 1)$ .

### 3. Diffusive systems

*The question.* Is there a systematic way of deriving the effective, slow-scale evolution of a diffusive system displaying a fast and a slow timescale? Under what conditions will the effective evolution follow a diffusive process?

#### 3.1. General case

Let us consider continuous diffusive processes. Such processes are widely used to model dynamics that are intrinsically of continuous nature as for example the motion of a Brownian particle in a fluid. In other cases, such description may result from the approximation of discrete dynamics as, for instance, the Van Kampen system size expansion [25] of a set of chemical reactions or the many particles limit of reaction networks giving the chemical Langevin equation [1] or the Kimura-Ohta equation in population genetics [57]. Again we will consider the case in which two well separated time scales are involved and make use of asymptotic techniques [6]. As we will show in the following, continuous systems can display a richer temporal structure and their effective evolution may take place on time scales slower than the ones that initially characterize the system. We will give an example from population genetics in which the effective equation takes place on the time scales of the original slower process, and one concerning Brownian motion that evolves on a time scale slower than the initial slow one. The general process we consider (see [22]) is described by the system of Itô stochastic differential equations coupling the fast variables  $Y_t$  to the slow ones  $X_t$

$$dX_t^i = u^i(X_t, Y_t, t)dt + \beta^{ij}(X_t, Y_t, t) \cdot dB_t^j \quad (81)$$

$$dY_t^a = \epsilon^{-1} z^a(X_t, Y_t, t)dt + \epsilon^{-1/2} \sigma^{ab}(X_t, Y_t, t) \cdot d\hat{B}_t^b \quad (82)$$

where  $i, j = 1, \dots, n$ ,  $a, b = 1, \dots, m$ ,  $B_t^j$  and  $\hat{B}_t^b$  are independent Wiener processes and  $\epsilon \ll 1$ . The explicit dependence on time is only on time scales  $O(\epsilon^0)$  or slower<sup>7</sup>. We are interested in the dynamics of  $X_t$  in the limit  $\epsilon \rightarrow 0$ .

Of course, one may consider different couplings and scaling between the slow and fast processes. A relevant case with alternative coupling can be used to investigate the white noise limit of a colored noise (see e.g. [58, 59, 60, 61, 62] for the general discussion on the interpretation of the resulting noise). The general idea there, is to separate the time-scale on which the relevant process takes place from the typical correlation time of the noise. An approach within the methods presented in the section was taken in [63] following the discussion provided in Gardiner's book [64]. More complex cases involving the interplay between the inertial time scale of a Brownian particle and the correlation of its noise were studied in [65, 6].

For the case we are considering, the Kolmogorov equations for the propagator  $p(x, y, t | x', y', t')$  read<sup>8</sup>

$$\partial_t p = L^\dagger p, \quad \partial_{t'} p = -L' p \quad (83)$$

where the  $'$  indicates the dependence on the initial variables  $x', y', t'$  and the generator of the diffusion process is

$$L = \underbrace{u^i \frac{\partial}{\partial x^i} + \frac{1}{2} d^{ij} \frac{\partial^2}{\partial x^i \partial x^j}}_{L_0} + \epsilon^{-1} \underbrace{\left( z^a \frac{\partial}{\partial y^a} + \frac{1}{2} g^{ab} \frac{\partial^2}{\partial y^a \partial y^b} \right)}_M \quad (84)$$

with

$$d^{ij} = \beta^{ik} \beta^{jk} \quad g^{ab} = \sigma^{ac} \sigma^{bc}. \quad (85)$$

<sup>7</sup>In general the drift of the fast variable may also contain terms of order  $O(\epsilon^0)$ . However, such terms behave regularly in the limiting procedure as we will see in the example concerning a force acting on a Brownian particle undergoing Langevin-Kramers dynamics as discussed in [21] and reported in section 3.2.2.

<sup>8</sup>Note that for diffusive processes we adhere to the usual notation in the mathematics literature that  $L$  is the generator of the process (backward) and  $L^\dagger$  is the (forward) Fokker-Planck operator. For discrete processes we have defined  $L$  as the forward operator instead (also customary in the physics literature).



We will perform the averaging procedure on the backward equation but the same approach can be applied to the forward one (as done for example in [21]). We start by introducing the fast and slow time variables  $\theta = \epsilon^{-1}t$  and  $\tilde{t} = \epsilon t$  and expand the solution as

$$p = p^{(0)} + \epsilon p^{(1)} + \epsilon^2 p^{(2)} + \dots \quad (86)$$

At order  $\epsilon^{-1}$  the backward equation reads

$$\left( \frac{\partial}{\partial \theta} + M \right) p^{(0)} = 0. \quad (87)$$

As for the discrete case we consider the case in which the fast dynamics relaxes on fast time scales to an equilibrium solution for any given value of the slow variable  $x$  and time  $t$

$$M^\dagger w_{eq}(x, y, t, \tilde{t}) = 0. \quad (88)$$

In general the averaging procedure can be carried out also for the case in which the fast process reaches a non-equilibrium steady state. We address such general case in Appendix B. The presence of a steady state implies that the spectrum of  $M^\dagger$  has a top eigenvalue  $E_0 = 0$  and we assume a finite gap ( $E_1 < 0$ ). As a consequence, after a fast transient, the solution will relax to a constant in  $y$ :

$$p^{(0)} = \rho(x, t, \tilde{t}). \quad (89)$$

*Propagator at order  $\epsilon^0$ .* At order  $\epsilon^0$  one has, after the initial relaxation,

$$Mp^{(1)} = -\left( \frac{\partial}{\partial t} + L_0 \right) p^{(0)}. \quad (90)$$

The solvability condition requires (as in the discrete case) the RHS to be orthogonal to the nullspace of  $M^\dagger$  which, according to eq. (88) is spanned by  $w_{eq}$ . Then, multiplying to the left by  $w_{eq}$  and integrating over  $y$  we have

$$0 = -\frac{\partial \rho}{\partial t} - \int dy w_{eq} L_0 \rho \quad (91)$$

where we have made use of  $\int dy w_{eq} = 1$ . Therefore

$$\frac{\partial \rho}{\partial t} + \bar{L}_0 \rho = 0 \quad (92)$$

and the generator of the slow process is

$$\bar{L}_0 = \bar{u}^i \frac{\partial}{\partial x^i} + \frac{1}{2} \bar{d}^{ij} \frac{\partial^2}{\partial x^i \partial x^j} \quad (93)$$

where  $\bar{\dots} = \int dy \dots w_{eq}$  denotes the average over the equilibrium distribution of the fast variables. This concludes the elimination unless the slow drift and diffusion coefficient average to zero on the equilibrium distribution of fast variables. At variance with the discrete case, this is possible and indeed happens, for instance, in the high friction limit of Brownian motion (see section 3.2.2).

*Propagator at order  $\epsilon$ .* In the case  $\bar{u}^i = 0$  and  $\bar{d}^{ij} = 0$  we need to proceed to the following order. The previous solvability condition then becomes

$$\frac{\partial \rho}{\partial t} = 0 \quad (94)$$

and the equation for  $p^{(1)}$  reduces to

$$Mp^{(1)} = -L_0 \rho = -u^i \frac{\partial \rho}{\partial x^i} - \frac{1}{2} d^{ij} \frac{\partial^2 \rho}{\partial x^i \partial x^j} \quad (95)$$

with formal solution

$$p^{(1)} = -M^{-1}L_0\rho + \text{zero modes of } M = -M^{-1}\left(u^i \frac{\partial \rho}{\partial x^i} + \frac{1}{2}d^{ij} \frac{\partial^2 \rho}{\partial x^i \partial x^j}\right) + \text{zero modes of } M. \quad (96)$$

The equation at order  $\epsilon$  is

$$\left(\frac{\partial}{\partial \theta} + M\right)p^{(2)} = -\left(\frac{\partial}{\partial t} + L_0\right)p^{(1)} - \frac{\partial}{\partial \tilde{t}}p^{(0)}. \quad (97)$$

From this expression it is clear that, in general, the effective equation will contain derivatives of  $\rho$  of order higher than 2 hence describing non-Markovian effective dynamics. However, as already discussed by [66], if the diffusion coefficient of the slow variable  $d^{ij}$  does not depend on the fast variable  $y$ , the higher-order derivatives vanish and the effective dynamics is Markovian. Since we have required  $\bar{d}^{ij} = 0$  we see that at order  $\epsilon$  the dynamics is Markovian only if there is no noise on the slow variable (i.e.  $d^{ij} = 0$ ). In such a case the solvability condition becomes an effective backward Kolmogorov equation on slow time scales

$$\frac{\partial \rho}{\partial \tilde{t}} + \underbrace{\left(u^j \frac{\partial}{\partial x^j} (-M^{-1}u^i)\right)}_{U^i} \frac{\partial \rho}{\partial x^i} + \underbrace{u^i (-M^{-1}u^j)}_{\frac{1}{2}\bar{D}^{ij}} \frac{\partial^2 \rho}{\partial x^i \partial x^j} = 0 \quad (98)$$

where we have made use of  $\overline{\partial_t M^{-1}f} = \partial_t \overline{M^{-1}f} = 0$  for any  $f$  such that  $\bar{f} = 0$  and assumed that  $w_{eq}$  depends on  $O(\epsilon)$  times only. We provide the proof which is a slight generalization of the one in Ref. [22] in appendix B. Relying on the fact that the fast dynamics reaches an equilibrium steady state (which amounts to say  $M^\dagger w_{eq} = w_{eq}M$  by detailed balance) one can show that, for any  $f$  and  $g$  with  $\bar{f} = \bar{g} = 0$

$$\overline{g(-M^{-1}f)} = \overline{f(-M^{-1}g)} \quad (99)$$

which defines a scalar product. The most immediate consequence is that this ensures that the diffusion coefficient is symmetric and positive

$$\frac{1}{2}D^{ij} = \overline{u^i (-M^{-1}u^j)}. \quad (100)$$

*Summary.* The effective evolution of a diffusive process involving a fast and a slow scale can be found with a systematic multiple scale approach. If the fast processes reach a steady state, the effective system will follow a diffusive process itself with a generator given by the average of the generator of the slow dynamics over the stationary distribution of the fast variables. If this average is zero, one obtains a diffusive effective evolution only if the initial system has no noise acting on the slow variables. In such a case the effective drift and diffusion coefficient are not simply an average of the initial slow ones but depend also on time-correlations of the slow drift at the steady state through the Green's function of the fast process.

### 3.2. Examples for diffusive dynamics

We shall present here two applications of the shown method. The first one is taken from population genetics and will have an effective dynamics taking place at order  $\epsilon^0$ . The second one is the high friction limit of Brownian motion and will require two separate time scales to obtain the relevant effective equations.

#### 3.2.1. Population genetics in changing fitness landscapes

The stochastic equation we consider comes from population genetics and describes the evolutionary process of a population under mutations, genetic drift and natural selection (see [67, 68, 69] for a general exposition). A key intuition for modeling the effects of natural selection is the concept of fitness of a population in a certain environment which describes the global ability of the population to reproduce and survive [70]. The different fitness of various genotypes can be effectively visualized in terms of a fitness landscape [71] which is usually "climbed" during the course of evolution. Such climbing is referred to as adaptation. Fisher's fundamental theorem of natural selection [72]

states that when evolution is subject only to natural selection in a constant environment, the fitness of a population increases at a positive rate equal to the variance of the population. Indeed, natural selection, by its very definition, is the force that favors fitter individuals, pushing towards the genotype configuration which maximizes the global fitness. When mutations and random drift are relevant, the stochastic nature of evolution emerges and adaptation becomes a more complex phenomenon. One of the most widely accepted model for the stochastic description of the evolutionary process is the Kimura-Ohta equation [57] that we will describe in detail in Eq. (102) below. In most natural cases the environment in which the population evolves changes in time (see for example Refs. [73, 74, 75, 76, 77, 78, 79, 80]) and genotypes that were fit under the initial condition may successively be unfavored by selection. Consider for instance the case of a population of bacteria shaped by natural selection to metabolize a certain nutrient. If such nutrient is gradually replaced by a different one for which metabolic enzymes are not genetically encoded, bacteria will now be less efficient and their fitness will decrease. At the same time adaptation to this new environment though mutations will start taking place and eventually lead to an increase in fitness. We can then represent the fitness dynamics as the result of two effects: adaptation driven by natural selection and fitness changes due to environmental variations:

$$\frac{d}{dt}\text{Fitness} = \text{Adaptation} + \text{Environmental changes} . \quad (101)$$

The changes brought about by the variability of the environment give a negative contribution countered by adaptation, which is, in general, positive.

We focus on the case in which the environment exerting natural selection on the population changes very rapidly and in a random fashion consequently alternatively favoring the different genotypes. Such limit of a very rapidly changing selection goes under the name of microevolutionary limit and was shown to give an effective diffusive equation on time scales that are much longer than the typical environment variation, a result first obtained more than four decades ago (see Refs. [81, 82]) We review this problem within the framework derived in the previous section, closely following Ref. [83]. For the sake of simplicity we consider the case in which the population can have two different genotypes:  $G$  and  $G'$  and denote by  $x$  the frequency of individuals of genotype  $G$  and by  $1 - x$  the one of  $G'$ . The Kimura-Ohta equation for a population that switches between two possible genotypes is equivalent to the following one dimensional Itô SDE

$$dX_t = \left( s(X_t, Y_t)X_t(1 - X_t) + m(X_t) \right) dt + \sqrt{\frac{1}{N}X_t(1 - X_t)} \cdot dB_t \quad (102)$$

where  $dB_t$  is a Wiener process,  $m(x) = -\mu x + \nu(1 - x)$  is the mutation coefficient,  $\mu$  and  $\nu$  are the mutation rates and  $N$  is the effective population size.  $s(x, y)$  is the selection coefficient, which describes the effect of natural selection and depends on the environmental state  $y$  and, in the simple case we are considering, can be used to define the global fitness of the population  $F(x, y)$  via:

$$s(x, y) = \frac{\partial F(x, y)}{\partial x} . \quad (103)$$

The environment follows the faster dynamics which, for the sake of simplicity, we assume to be an Ornstein-Uhlenbeck process with constant diffusion  $D$  and spring constant  $K$  (of order 1)

$$dY_t = -\epsilon^{-1}KY_t dt + \epsilon^{-1/2}\sqrt{2D} \cdot d\hat{B}_t \quad (104)$$

where  $d\hat{B}_t$  is a Wiener process and  $\epsilon \ll 1$  is the parameter accounting for the time-scale separation between the environment and the genotype evolution. At the steady state  $\bar{y} = 0$  and  $\bar{y}^2 = D/K$ . For the sake of exemplification we consider the case in which the selection coefficient has a simple linear dependence on the environment and does not depend on the genotype frequency:  $s(y) = \sigma y$ . This implies that a positive environmental state favors genotype  $G$  whereas a negative one favors  $G'$ . The fitness of the population, up to an arbitrary constant, is then:

$$F(x, y) = \sigma xy . \quad (105)$$

In the notation of the previous section we have that the drift of the slow process is

$$u(x, y) = s(x, y)g(x) + m(x) = \sigma yx(1 - x) - \mu x + \nu(1 - x) \quad (106)$$

and the diffusion matrix does not depend on the fast process

$$d(x) = \frac{1}{N}x(1-x).$$

Since the only term in the slow drift depending on the fast process is linear in  $y$  and  $\bar{y} = 0$  we have that the effective drift on the slow time-scale reads

$$\bar{u} = -\mu x + \nu(1-x) \quad (107)$$

and is independent of the selection coefficient. This concludes our elimination procedure and shows that the effective dynamics is described by

$$dX_t = m(X_t)dt + \sqrt{\frac{1}{N}X_t(1-X_t)} \cdot dB_t \quad (108)$$

and apparently neutral: *i.e.*, not subject to selection.

*Summary.* Within a simple single-locus two-allele model of population genetics we have considered the evolution of a genotype in presence of a rapidly changing stochastic environment. The allele frequency follows a diffusive equation with a selection coefficient that is given by the average selection exerted by the environment.

### 3.2.2. From Langevin-Kramers dynamics to Brownian motion

We then move to an example in which the effective dynamics takes place on a time-scale which is much slower than the one of the original system. We shall discuss the high friction limit of Langevin-Kramers dynamics describing the motion of a microscale particle immersed in a fluid. This is a rather well studied system (see [84] for a pedagogical exposition) when the temperature of the fluid is constant. Here we consider the case in which both the temperature and the viscous friction of the fluid can vary smoothly in space. The initial equations are the ones in Eq. (1). Here we consider also the possibility of an external force  $f$  acting on the particle and, in order to have a more concise notation, we adopt a non-dimensional expression by introducing the following rescalings:

$$\begin{aligned} X &\rightarrow \frac{X}{L} & V &\rightarrow V \sqrt{\frac{m}{k_B T_0}} & f &\rightarrow \frac{f}{k_B T_0 / L} \\ T &\rightarrow \frac{T}{T_0} & t &\rightarrow t \frac{\sqrt{k_B T_0 / m}}{L} & \gamma &\rightarrow \frac{\gamma L}{\sqrt{k_B T_0 m}} \end{aligned} \quad (109)$$

where  $T_0$  is a reference temperature,  $k_B$  the Boltzmann constant,  $m$  the mass of the particle and  $L$  the typical length scale of the process. We are interested in deriving the strong friction limit of the Kolmogorov equation. To keep track of this limiting procedure we express the friction as  $\gamma \rightarrow \epsilon^{-1}\gamma$ . We then have

$$\begin{aligned} dX_t^i &= V_t^i dt \\ dV_t^i &= f^i(X_t, t)dt - \epsilon^{-1}\gamma(X_t, t)V_t^i dt + \epsilon^{-1/2} \sqrt{2T(X_t, t)\gamma(X_t, t)} d\hat{B}_t^i \end{aligned} \quad (110)$$

where  $\hat{B}_t^i$  are independent Wiener processes. The validity and limitation of such starting model are investigated in Ref. [85] within a fluctuating hydrodynamics approach with special attention to the long range correlations of a fluid subject to a temperature gradient. Here, the diffusion coefficient multiplying the noise term does not depend on velocity so, at this level, there is no need to specify the discretization prescription (Itô, Stratonovich or others). In the following we shall abridge the notation by omitting the explicit dependency on the trajectory, e.g.  $f^i(X_t, t) \equiv f_t^i$ . This set of equations is richer than the one discussed in the general example since the fast variable  $v$  has also a slow contribution to its drift (given by the external force  $f$ ). As we shall see in the following this will not impact on our elimination procedure. In order to keep as close as possible to the general example discussed above we consider the backward Kolmogorov equation. The complementary forward case is described in [21]. The backward equation is

$$\left( \frac{\partial}{\partial t} + L_0 + \epsilon^{-1}M \right) p_t = 0 \quad (111)$$

where

$$L_0 = v_t^i \frac{\partial}{\partial x^i} + f_t^i \frac{\partial}{\partial v^i} \quad M = \gamma_t \left[ -v_t^i \frac{\partial}{\partial v^i} + T_t \frac{\partial}{\partial v^i} \frac{\partial}{\partial v^i} \right]. \quad (112)$$

As usual we introduce a fast time variable  $\theta = \epsilon^{-1}t$ , associated to frictional relaxation. We also define a very slow one  $\tilde{t} = \epsilon t$ , the time-scale of variation of temperature and friction. The propagator is assumed to be a function of fast, slow and very slow times, and developed in power series in  $\epsilon$  as  $p = p^{(0)} + \epsilon p^{(1)} + \epsilon^2 p^{(2)} \dots$

*Fast time scales..* Here we show that the dynamics at fast time scales (of the order of the inverse friction) is ruled by the balance of thermal noise and friction, and leads to relaxation to the Maxwell-Boltzmann distribution in velocity space, with the local temperature. After the initial relaxation, at order  $\epsilon^{-1}$  the forward Kolmogorov equation reads

$$M^\dagger w_{eq} = 0 . \quad (113)$$

For the case we are considering the eigenfunctions of  $M^\dagger$  are products of Hermite polynomials in the velocity variable multiplied by the weight

$$w_{eq} = \frac{\exp\left(-\frac{v^2}{2T}\right)}{(2\pi T)^{n/2}} \quad (114)$$

i.e. the local Maxwellian equilibrium,

$$\psi_{k_1, \dots, k_n} = w \prod_{i=1}^n H_{k_i}(v^i / \sqrt{T}) \quad M \psi_{k_1, \dots, k_n} = -\gamma \left( \sum_{i=1}^n k_i \right) \psi_{k_1, \dots, k_n} \quad (115)$$

with  $k_i = 0, 1, \dots$ . Since the spectrum is nonnegative, the solution relaxes exponentially fast to the zero eigenfunction for  $\theta \rightarrow \infty$ . The solution of the backward equation at order  $\epsilon^{-1}$  then has to be constant in the velocity variables

$$p^{(0)}(x, v, t, \tilde{t}) = \rho(x, t, \tilde{t}) \quad (116)$$

where  $\rho$  is the marginal probability density in space, at lowest order.

*Slow time scales..* As we know from the general formalism (see eq. 92) on slow time scales the dynamics is determined by the average of the slow operator  $\overline{L_0}$ . For the system under consideration  $\overline{L_0} = 0$  so that the effective equation on the slow time-scale reads

$$\frac{\partial \rho}{\partial t} = 0 \quad (117)$$

implying that the dependence on time for  $\rho$  is only through the very slow time-scale  $\tilde{t}$ , i.e.  $p^{(0)}$  reaches a quasi-steady-state at slow time scales where the dependence on very slow time scales enters as a parameter only.

To proceed further we need to derive the explicit expression of  $p^{(1)}$  from the equation on slow time scales at order  $\epsilon^0$

$$M p^{(1)} = -L_0 p^{(0)} . \quad (118)$$

Noticing that

$$M v^i = -\gamma v^i \quad (119)$$

and making use of the explicit expression of  $L_0$  one obtains

$$p^{(1)} = -M^{-1} L_0 p^{(0)} = \frac{1}{\gamma} v^i \frac{\partial}{\partial x^i} \rho + r \quad (120)$$

where  $r = r(x, \tilde{t})$  is the contribution from the null-space of  $M$ .

*Very slow time scales..* At these scales we obtain the overdamped dynamics in position space as follows. At order  $\epsilon^1$ , after relaxation over fast variables, the solvability condition is obtained by integrating both sides over  $w_{eq}$  and provides the description on the very slow dynamics

$$\frac{\partial}{\partial \tilde{t}} p^{(0)} + \overline{L_0 p^{(1)}} = 0 \quad (121)$$

which gives

$$\frac{\partial \rho}{\partial t} + \frac{f^i}{\gamma} \frac{\partial \rho}{\partial x^i} + T \frac{\partial}{\partial x^i} \frac{1}{\gamma} \frac{\partial \rho}{\partial x^i} = 0 . \quad (122)$$

This corresponds to the overdamped stochastic differential equation

$$dX_t^i = \left( \frac{f^i}{\gamma} - \frac{1}{2\gamma} \frac{\partial T}{\partial x^i} + \frac{T}{2} \frac{\partial \gamma^{-1}}{\partial x^i} \right) dt + \sqrt{\frac{2T}{\gamma}} \circ dW_t^i \quad (\text{Stratonovich}) \quad (123)$$

or, in Itô form,

$$dX_t^i = \left( \frac{f^i}{\gamma} + T \frac{\partial \gamma^{-1}}{\partial x^i} \right) dt + \sqrt{\frac{2T}{\gamma}} \cdot dW_t^i \quad (\text{Itô}) \quad (124)$$

We have then completed the averaging of the velocities degrees of freedom and obtained the dynamics taking place on the very slow time scales involving only the position variables. This description displays corrections of order  $\epsilon$  and was also derived with a different approach in Ref. [86]. We note that, if friction is constant, the equation reduces to a Itô stochastic differential equation with drift  $f^i/\gamma$ :

$$\frac{\partial \gamma}{\partial x^i} = 0 \quad dX_t^i = f^i/\gamma \, dt + \sqrt{2T(x_t)/\gamma} \cdot dW_t^i \quad (\text{Itô}) \quad (125)$$

in agreement with [87, 88, 89]. When, instead, temperature is constant we recover the result obtained e.g. in [90] (see e.g. [62] for a review).

*Summary.* The large-friction (or small-mass) limit of a microscopic particle diffusing in a fluid can be derived using multiple-scale techniques. When the temperature and friction are uniform in space, the result is the well-known overdamped approximation. For space-dependent temperature and friction diffusion, these techniques provide the physically correct interpretation of the multiplicative noise that appears in the overdamped approximation.

## Part II

# Functionals

### 4. Paths and sequential observables of discrete Markov processes

*The question.* We have seen how to obtain the effective slow evolution of a discrete Markov process. Can the same procedure be applied to a functional of the stochastic trajectory such as entropy production, counting statistics, fluxes, etc...? Will it be possible to express the evolution of a generic functional in terms of the effective states and their dynamics?

#### 4.1. General functional of the discrete dynamics

*From the master equation to the path-integral*

For a system jumping between discrete states with given transition rates the probability density of observing a given path takes a rather simple expression. This is because we can decompose such probability as the product of probabilities of each successive step. For instance the probability density of observing the sequence of states  $\{i \text{ in } (t' = \tau_0, \tau_1); j \text{ in } (\tau_1, \tau_2); \dots\}$  is expressed as the product of the probability of not exiting state  $i$  until time  $\tau_1$  times the transition rate from  $i$  to  $j$   $K_i^j$  times the probability of remaining in state  $j$ :

$$\mathcal{P}_{\tau_2, t'} = \exp[-(\tau_1 - \tau_0)e_i] K_i^j \exp[-(\tau_2 - \tau_1)e_j] \quad (126)$$

where we recall that  $e_i$  is the exit rate from state  $i$  as defined in section 2. In general, a trajectory of the discrete Markov process is given by the sequence of states

$$i(\tau) \quad t' \leq \tau \leq t$$

or, making the transitions explicit

$$\{i_0 \text{ in } (t' = \tau_0, \tau_1); \dots; i_k \text{ in } (\tau_k, \tau_{k+1}); \dots; i_N \text{ in } (\tau_N, \tau_{N+1} = t)\}$$

The probability density of having undergone exactly  $N$  transitions at times  $\tau_1, \dots, \tau_N$  before time  $t$ , with a sequence of states  $i_1 \dots i_N$ , starting from initial state  $i_0$ , decays in time due to outbound transitions from the final state

$$\frac{\partial}{\partial t} \mathcal{P}_{t, t'}^N(\tau_1 i_1, \dots, \tau_N i_N | i_0) = -e_{i_N} \mathcal{P}_{t, t'}^N(\tau_1 i_1, \dots, \tau_N i_N | i_0)$$

for  $t > \tau_N$ . The initial condition (at time  $t = \tau_N$ ) for the above equation is

$$\mathcal{P}_{\tau_N, t'}^N(\tau_1 i_1, \dots, \tau_N i_N | i_0) = \mathcal{P}_{\tau_N, t'}^{N-1}(\tau_1 i_1, \dots, \tau_{N-1} i_{N-1} | i_0) K_{i_{N-1}}^{i_N}$$

i.e. the probability of having undergone  $N - 1$  transitions at the specified times up to time  $\tau_N$  and a new transition at time  $\tau_N$ . The density  $\mathcal{P}^N$  has dimension  $\text{time}^{-N}$  and the rate  $K$  has dimension  $\text{time}^{-1}$ .

It follows that

$$\mathcal{P}_{t, t'}^N(\tau_1 i_1, \dots, \tau_N i_N | i_0) = \exp\left[-\int_{\tau_N}^t e_{i_N} d\tau + \log K_{i_{N-1}}^{i_N}\right] \mathcal{P}_{\tau_N, t'}^{N-1}(\tau_1 i_1, \dots, \tau_{N-1} i_{N-1} | i_0)$$

and proceeding recursively one finally has

$$\mathcal{P}_{t, t'}^N = \exp(-\mathcal{A}_{t, t'}^N)$$

with the action defined as

$$\mathcal{A}_{t, t'}^N = \sum_{k=1}^{N+1} \int_{\tau_{k-1}}^{\tau_k} d\tau e_{i_{k-1}} - \sum_{k=1}^N \log K_{i_{k-1}}^{i_k}. \quad (127)$$

Recall that this is a function of the  $N$  transition times and states, given the initial state. The normalization

$$\sum_{N=0}^{\infty} \sum_{i_1} \cdots \sum_{i_N} \int_{t'}^t d\tau_1 \int_{\tau_1}^t d\tau_2 \cdots \int_{\tau_{N-1}}^t d\tau_N \mathcal{P}_{t,t'}^N = 1$$

follows from noticing that

$$\sum_{N=0}^{\infty} \sum_{i_1} \cdots \sum_{i_N} \int_{t'}^t d\tau_1 \int_{\tau_1}^t d\tau_2 \cdots \int_{\tau_{N-1}}^t d\tau_N \mathcal{P}_{t,t'}^N(\tau_1 i_1, \dots, \tau_N i_N | i_0) \delta_{i_N}^j = p_{i_0}^j$$

#### Functionals of the trajectory

Let us turn our attention to the study of functionals of the stochastic trajectory. Such functionals can depend on the time spent in a given state and on the transitions occurred. In general one can write

$$\mathcal{J}_{t,t'} = \sum_{k=1}^{N+1} \int_{\tau_{k-1}}^{\tau_k} d\tau f_{i_{k-1}} + \sum_{k=1}^N g_{i_{k-1}}^{i_k} \quad (128)$$

where  $g_b^a$  is different from zero only if a transition occurs, i.e.  $a \neq b$ . Relevant instances of such a functional are the residence time in a given state  $j$  ( $f_i = \delta_{ij}$  and  $g = 0$ ), the transition counting statistics from  $j$  to  $j'$  ( $f = 0$  and  $g_i^{i'} = \delta_{ij'}^j$ ) as well as the action of the process (127) or the entropy production (see section 4.3). Notice that if  $g_b^a = \phi_a - \phi_b$  then the last sum above is telescopic and it reduces to the evaluation of boundary terms.

The value of the functional  $\mathcal{J}_{t'}$  undergoes both smooth changes and jumps. The probability  $p^i(J)$  of being in state  $i$  at time  $t$  with a value of the integral  $\mathcal{J}_t = J$  is given by the solution of the equation

$$\frac{d}{dt} p^i(J) = -\frac{\partial}{\partial J} f_i p^i(J) + \sum_j (K_j^i p^j(J - g_j^i) - K_i^j p^j(J)) \quad (129)$$

Introducing the generating function of  $J$  along trajectories that end in state  $i$  at time  $t$

$$G^i(s) = \int_{-\infty}^{\infty} dJ e^{-sJ} p^i(J)$$

one has

$$\frac{d}{dt} G^i = \sum_j [K_j^i \exp(-s g_j^i) G^j - (K_i^j + s f_i \delta_i^j) G^i] \equiv \sum_j H_j^i G^j \quad (130)$$

evolving under the action of the tilted generator  $H$ . The modified generator is given by the original one with the off-diagonal terms multiplied by  $\exp(-s g_j^i)$  and additional  $s f_i$  on the diagonal. Setting  $s = 0$  one recovers the original dynamics. Notice that the long time limit of eq. (129) and (130) contain the same information of the large deviation function of  $J$  (see e.g. [91]).

#### 4.1.1. Averaging functionals, discrete case

As we have done for the dynamics, we shall seek an effective evolution of the generating function of the functional on the slower time scales. As a first step we shall decompose the tilted generator in its slow and fast components

$$H = \epsilon^{-1} M_s + H^{(0)}. \quad (131)$$

For the six states example discussed in section 2 and described in figure 2, the fast tilted generator reads

$$\tilde{M}_s = \left( \begin{array}{cc|cc|c} - (F_3^1 + F_3^4 + F_3^5) & F_4^3 e^{-s g_4^3} & & & \\ F_3^4 e^{-s g_3^4} & -F_4^3 & & & \\ \hline F_3^5 e^{-s g_3^5} & 0 & -F_5^6 & & \\ F_3^1 e^{-s g_3^1} & 0 & 0 & -F_1^2 & F_2^1 e^{-s g_2^1} \\ 0 & 0 & 0 & F_1^2 e^{-s g_1^2} & -F_2^1 \\ \hline 0 & 0 & F_5^6 e^{-s g_5^6} & 0 & 0 & 0 \end{array} \right) \quad (132)$$



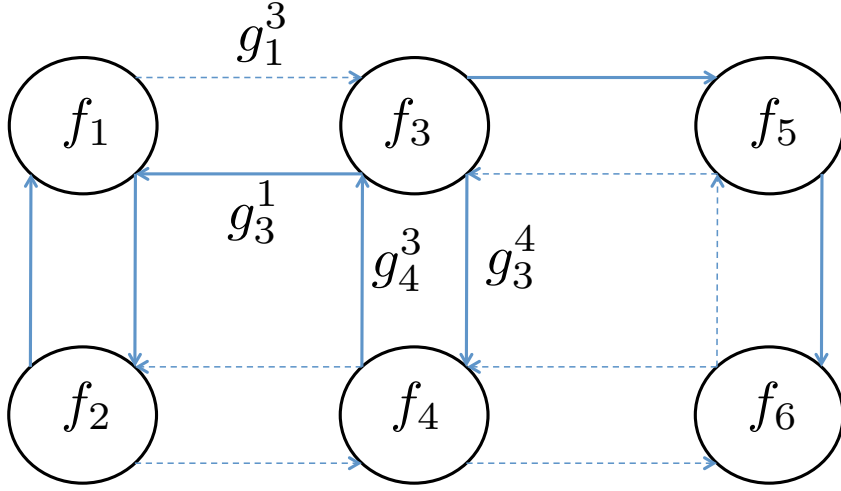


Figure 20: Functional of the continuous-time Markov chain involving 6 states depicted in figure 2. The quantities  $g_i^j$  represent the change of the functional upon transitions from state  $i$  to  $j$  whereas  $f_i$  is the contribution picked up while residing in state  $i$

where the superscript  $\sim$  is used to recall that we have ordered the states to have a block triangular structure as in eq. (8), *i. e.*, (3, 4, 5, 1, 2, 6). The slow modified generator is given by

$$\tilde{L}^{(0)} = \begin{pmatrix} -sf_3 & 0 & S_5^3 e^{-sg_5^3} & S_1^3 e^{-sg_1^3} & 0 & 0 \\ 0 & -sf_4 - S_4^2 - S_4^6 & 0 & 0 & S_2^4 e^{-sg_2^4} & S_6^4 e^{-sg_6^4} \\ 0 & 0 & -sf_5 - S_5^3 & 0 & 0 & S_6^5 e^{-sg_6^5} \\ 0 & 0 & 0 & -sf_1 - S_1^3 & 0 & 0 \\ 0 & S_4^2 e^{-sg_4^2} & 0 & 0 & -sf_4 - S_4^4 & 0 \\ 0 & S_4^6 e^{-sg_4^6} & 0 & 0 & 0 & -sf_6 - S_6^4 - S_6^5 \end{pmatrix} \quad (133)$$

This is schematically depicted in figure 20 where it is highlighted that the functional changes of an amount  $g_i^j$  in a transition from  $i$  to  $j$  and that it increases while in state  $i$  at a rate  $f_i$ . At order  $\epsilon^{-1}$  one has

$$\frac{d}{d\theta} \mathbf{G}^{(0)} = \mathbf{M}_s \mathbf{G}^{(0)}. \quad (134)$$

In order to have a stationary state we need to require the eigenvalues of  $\mathbf{M}_s$  to have non-positive real part. This was granted for the unperturbed generator of the dynamics  $\mathbf{M}$ . Here, the presence of the additional exponential terms may lift the zero eigenvalues of  $\mathbf{M}$  to positive values. Indeed, for the case at hand, the largest eigenvalue of block  $a$  (involving state 1 and 2), which was 0 for the generator of the dynamics, takes the following form:

$$\lambda_a(s) = \frac{1}{2} \left[ -(F_2^1 + F_1^2) + \sqrt{(F_2^1 + F_1^2)^2 - 4F_2^1 F_1^2 (1 - e^{-(g_1^2 + g_2^1)s})} \right] \quad (135)$$

so that to ensure the steady state we shall require  $g_1^2 = g_2^1 = 0$ . This corresponds to saying that, in order to perform the averaging procedure discussed for the dynamics, we must choose functionals that do not depend on the fast transitions within the blocks that will be part of the effective dynamics. This is not surprising since the number of such contributions before a slow transition occurs would be extremely large (order  $\epsilon^{-1}$ ).<sup>9</sup> We can then proceed to evaluate the steady state and find it to be

$$\mathbf{G}^{(0)} = q_a \tilde{w}_a + q_d \tilde{w}_d \quad (136)$$

where  $q_a$  and  $q_d$  are generic positive functions and  $\tilde{w}_a, \tilde{w}_d$  are the eigenvectors spanning the right null space of  $\mathbf{M}_s$ . They coincide (modulo the state reshuffling giving the block triangular structure) with the eigenvectors of the unperturbed generator  $\mathbf{M}$  introduced in eq. (11).

At order  $\epsilon^0$

$$\frac{d\mathbf{G}^{(1)}}{d\theta} + \frac{d\mathbf{G}^{(0)}}{dt} = \mathbf{M}_s \mathbf{G}^{(1)} + \mathbf{H}^{(0)} \mathbf{G}^{(0)}$$

the solvability condition is obtained by multiplying by the eigenvectors spanning the left nullspace of  $\mathbf{M}_s$ :

$$\begin{aligned} \tilde{v}_s^a &= \left( \frac{F_3^1 e^{-s g_3^1}}{F_3^1 + (1 - e^{-s(g_4^3 + g_3^4)})F_3^4 + F_3^5}, e^{-s g_4^3} \frac{F_3^1 e^{-s g_3^1}}{F_3^1 + (1 - e^{-s(g_4^3 + g_3^4)})F_3^4 + F_3^5}, 0, 1, 1, 0 \right) \\ \tilde{v}_s^d &= \left( \frac{F_3^5 e^{-s(g_3^5 + g_5^6)}}{F_3^1 + (1 - e^{-s(g_4^3 + g_3^4)})F_3^4 + F_3^5}, e^{-s g_4^3} \frac{F_3^5 e^{-s(g_3^5 + g_5^6)}}{F_3^1 + (1 - e^{-s(g_4^3 + g_3^4)})F_3^4 + F_3^5}, e^{-s g_5^6}, 0, 0, 1 \right) \end{aligned} \quad (137)$$

where it can be seen that, setting  $s = 0$ , one recovers the left eigenvectors of the unperturbed generator as in eq. (16) apart from the reordering of states.

The entries in (137) can be understood as the generating functions for the functional  $J$  along the fast dynamics, conditioned on absorption in a block. Developing the fractions as geometric series one finds, for instance

$$\frac{F_3^1 e^{-s g_3^1}}{F_3^1 + F_3^4 (1 - e^{-s(g_4^3 + g_3^4)}) + F_3^5} = \frac{F_3^1}{F_3^1 + F_3^4 + F_3^5} \sum_{n=0}^{\infty} \left( \frac{F_3^4}{F_3^1 + F_3^4 + F_3^5} \right)^n e^{-s(g_3^1 + n g_4^3 + n g_3^4)} \quad (138)$$

On the right-hand side, the prefactor is the probability of exiting from 3 to 1, the factor within brackets is the probability of going from 3 to 4,  $n$  is the number of transits from 3 to 4, which also equals the number of transits from 4 to 3 since the probability of going from 3 to 4 is unity.  $g_3^1 + n g_4^3 + n g_3^4$  is the value of the functional along a fast path that starts in 3 and ends in 1 after  $n$  returns to 3. The effective equation then reads

$$\begin{aligned} \frac{dq_a}{dt} &= \frac{F_3^1 e^{-s g_3^1}}{F_3^1 + (1 - e^{-s(g_4^3 + g_3^4)})F_3^4 + F_3^5} \left[ (w^{a_1} S_1^3 e^{-s g_3^1} + w^{a_2} S_2^4 e^{-s(g_2^4 + g_4^3)}) q_a + e^{-s(g_6^4 + g_4^3)} S_6^4 q_d \right] \\ &\quad - \left[ w^{a_1} (S_1^3 + s f_1) + w^{a_2} (S_2^4 + s f_2) \right] q_a \\ \frac{dq_d}{dt} &= \frac{F_3^5 e^{-s(g_3^5 + g_5^6)}}{F_3^1 + (1 - e^{-s(g_4^3 + g_3^4)})F_3^4 + F_3^5} \left[ (w^{a_1} S_1^3 e^{-s g_3^1} + w^{a_2} S_2^4 e^{-s(g_2^4 + g_4^3)}) q_a + e^{-s(g_6^4 + g_4^3)} S_6^4 q_d \right] \\ &\quad + e^{-s(g_6^5 + g_5^6)} S_6^5 q_d - (S_6^4 + S_6^5 + s f_6) q_d \end{aligned} \quad (139)$$

Developing the denominator as geometric series as discussed above one finds that the effective equations can be

<sup>9</sup>Note that one may allow functionals that depend on such transitions but admit a steady state. However, additional requirements on the specific form of the functional must be made. In the current example, choosing  $g_1^2 = -g_2^1$  would grant a steady state. More generally, the condition to be satisfied is that changes in the functional occurring while the system is within one absorbing block must always sum to zero.

written as follows

$$\begin{aligned}
\frac{dq_a}{dt} &= w^{a_1} S_1^3 e^{-sg_1^3} \sum_{path \in A_{3 \rightarrow a}} \text{Prob}[path] e^{-s\Delta J[path]} q_a + w^{a_2} S_2^4 e^{-sg_2^4} \sum_{path \in A_{4 \rightarrow a}} \text{Prob}[path] e^{-s\Delta J[path]} q_a \\
&\quad + S_6^4 e^{-sg_6^4} \sum_{path \in A_{4 \rightarrow a}} \text{Prob}[path] e^{-s\Delta J[path]} q_d - w^{a_1} S_1^3 q_a - w^{a_2} S_2^4 q_a - s(w^{a_1} f_1 + w^{a_2} f_2) q_a \\
\frac{dq_d}{dt} &= w^{a_1} S_1^3 e^{-sg_1^3} \sum_{path \in A_{3 \rightarrow d}} \text{Prob}[path] e^{-s\Delta J[path]} q_a + w^{a_2} S_2^4 e^{-sg_2^4} \sum_{path \in A_{4 \rightarrow d}} \text{Prob}[path] e^{-s\Delta J[path]} q_a \\
&\quad + S_6^4 e^{-sg_6^4} \sum_{path \in A_{4 \rightarrow d}} \text{Prob}[path] e^{-s\Delta J[path]} q_d + S_6^5 e^{-sg_6^5} \sum_{path \in A_{5 \rightarrow d}} \text{Prob}[path] e^{-s\Delta J[path]} q_d \\
&\quad - S_6^4 q_d - S_6^5 q_d - s f_6 q_d
\end{aligned} \tag{140}$$

where by  $A_{k \rightarrow a}$  we have defined the set of fast paths (i.e. sequences of states connected by fast transitions only) that join state  $k$  to the absorbing block  $a$  (resp.  $d$ ).

As an example, let us consider the paths that from 3 are absorbed into  $a$

$$A_{3 \rightarrow a} = \left\{ (3, 1), (3, 4, 3, 1), (3, 4, 3, 4, 3, 1), \dots, \underbrace{(3, 4, \dots, 3, 4, 3, 1)}_{n \text{ times}}, \dots \right\} \tag{141}$$

with probabilities

$$\text{Prob} \left[ \underbrace{(3, 4, \dots, 3, 4, 3, 1)}_{n \text{ times}} \right] = \frac{F_3^1}{F_3^1 + F_3^4 + F_3^5} \left( \frac{F_3^4}{F_3^1 + F_3^4 + F_3^5} \right)^n \tag{142}$$

and changes in value for the functional  $J$

$$\Delta J \left[ \underbrace{(3, 4, \dots, 3, 4, 3, 1)}_{n \text{ times}} \right] = n g_3^4 + n g_4^3 + g_3^1 \tag{143}$$

Note that

$$\sum_{path \in A_{3 \rightarrow a}} \text{Prob}(path) + \sum_{path \in A_{3 \rightarrow d}} \text{Prob}(path) = 1$$

The interpretation of the effective process described by (140) is now straightforward. Let us assume the process is in block  $a$ . With probability  $w^{a_1} S_1^3 dt$  it can jump to visit 3 but then it immediately reverts back to  $a$  or moves to  $d$ . Among all possible fast paths that connect 3 to the absorbing states pick one with probability  $\text{Prob}(path)$ , and add the corresponding  $\Delta J[path]$  to the value of the functional. Independently, with probability  $w^{a_2} S_2^4 dt$ , it can jump to 4 and then again eventually get back to  $a$  or move to  $c$  through the corresponding fast paths. If there is no jump, the process stays in  $a$  and adds  $(w^{a_1} f_1 + w^{a_2} f_2) dt$  to the functional. The reasoning is similar for block  $d$ .

#### 4.1.2. Algorithm for the effective process

The procedure detailed above for a particular example in fact applies to all processes with fast and slow transitions and for general functionals  $J$ . Without repeating the calculations in general, here we provide an algorithm that generates the effective joint process for states and values of the functional:

- 1 Identify the absorbing blocks as discussed for the dynamics in Section 2 and compute the steady-state distributions (right-nullspace of  $M$ ). Check that the  $g_j^k$  within each block are zero.
- 2 Choose an initial condition for the effective process, say block  $a$  and set  $J = 0$ .
- 3 Extract an exponentially distributed time  $\tau$  with rate  $\sum_{i,j} w^{a_i} S_{a_i}^j$ .
- 4 Add  $\tau \sum_i f_{a_i} w^{a_i}$  to  $J$  and move time ahead by  $\tau$ .
- 5 Single out a slow transition channel  $a_i \rightarrow j$  according to a probability  $\pi_{a_i}^j = w_{a_i} S_{a_i}^j / \sum_{i,j} w_{a_i} S_{a_i}^j$ . Add  $g_{a_i}^j$  to  $J$ .

- 6 If  $j$  is outside  $a$ , pick a fast transition from  $j$  to  $k$  with the corresponding probability  $F_j^k / \sum_k F_j^k$ . Add  $g_j^k$  to  $J$  and iterate this step until the path ends in an absorbing block.
- 7 Cycle back to 3 until desired

The remarkable property of this algorithm is that time advances only on slow time-scale. The only added cost for computation is the construction of the sequence of fast states from one absorbing block to another or to itself, with only one slow transition out of the initial block.

*Summary.* It is possible to derive the effective evolution of a functional on the slow scales but, in general, it cannot be written in terms of the effective rates and blocks that described the slow effective dynamics. The characterization of the slow dynamics of a functional generally requires additional information. Namely, which specific channel was chosen to jump from one block to another and which path through eliminated states was taken.

#### 4.2. Functionals of block-diagonal fast dynamics

*The question.* Which simplifications in the effective equation for a functional are brought about by a block-diagonal structure of the fast transitions?

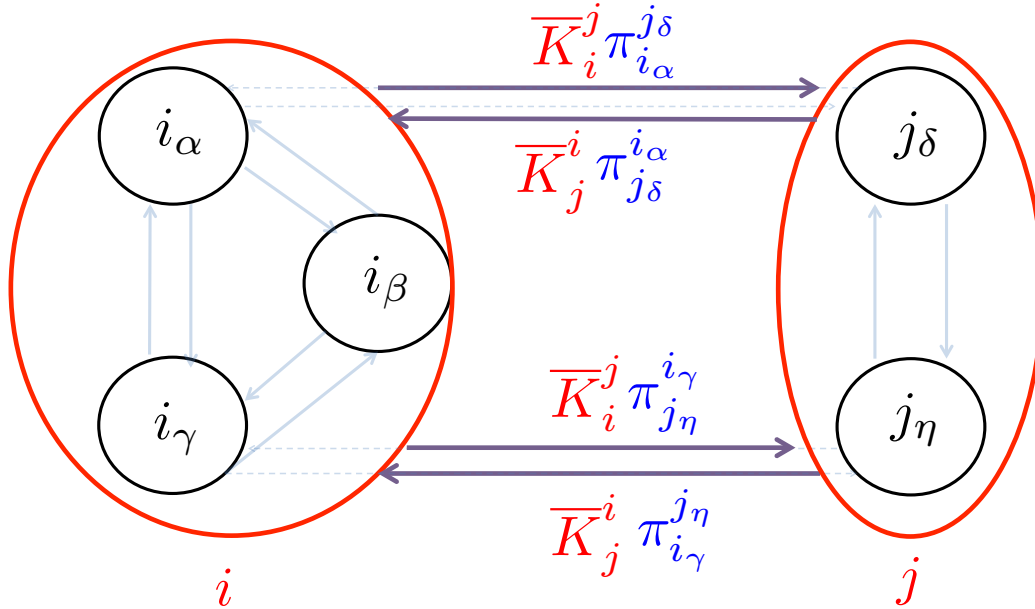


Figure 21: Block-diagonal dynamics and transition channels. In order to correctly describe a generic functional of the trajectories the different transition channels and their probabilities must be duly accounted for.

As we have seen when discussing the dynamics of discrete state Markov chains in section 2.2, the presence of a block-diagonal structure for the fast transitions allows to identify blocks of states that are connected only by slow transitions and simplifies the averaging procedure. The same applies for the study of functionals of the dynamics. We will focus on functionals that do not vary when transitions between fast states within a block occur:

$$g_{i\beta}^{i\alpha} = 0 \quad (144)$$

where, again, the latin indices label the block to which a state belong and the greek ones the specific fast state within the block (see Fig. 21). This implies that the fast part of the tilted generator describing the evolution of the generating function (eq. 131) is equal to the generator of the dynamics  $M_s = M$ . In this case, the stationary solution of the first order approximation to the generating function is

$$G_{m\mu}^{(0)i\alpha} = q_m^i w^{i\alpha} \quad (145)$$

At order  $\epsilon^0$  the equation then reads

$$\frac{dG^{(1)}}{d\theta} + \frac{dG^{(0)}}{dt} = MG^{(1)} + H^{(0)}G^{(0)}. \quad (146)$$

Due to the simple structure of the left null-space of the fast operator in the block-diagonal case (see eq. 28), the solvability condition is obtained by summing over the fast states

$$\frac{dq_m^i}{dt} = \sum_{j,\alpha,\beta} \bar{K}_j^i \pi_{j\beta}^{i\alpha} \exp(-s g_{j\beta}^{i\alpha}) q_m^j - \left( \sum_k \bar{K}_i^k + s \bar{f}_i \right) q_m^i \quad (147)$$

where

$$\pi_{j\beta}^{i\alpha} = \frac{S_{j\beta}^{i\alpha} w^{j\beta}}{\bar{K}_j^i}$$

are positive normalized weights ( $\sum_{\alpha,\beta} \pi_{j\beta}^{i\alpha} = 1$  for all  $i, j$ ) representing the *conditional probability* of the specific transition from  $i\alpha$  to  $j\beta$  given that a transition from block  $i$  to block  $j$  has occurred, in the limit  $\epsilon \rightarrow 0$ .

Inverting the Laplace transform, one obtains the effective master equation for the probability of being in state  $i$  given the initial state  $m$ , with a value  $J$  of the functional reads

$$\frac{dP_m^i(J)}{dt} = -\frac{\partial}{\partial J} \bar{f}_i P_m^i(J) + \sum_{j,\alpha,\beta} \left( \chi_{j\beta}^{i\alpha} P_m^j(J - g_{j\beta}^{i\alpha}) - \chi_{i\alpha}^{j\beta} P_m^i(J) \right) \quad (148)$$

where the rate for a jump  $g_{j\beta}^{i\alpha}$  in the value of the functional is

$$\chi_{j\beta}^{i\alpha} = \bar{K}_j^i \pi_{j\beta}^{i\alpha} = S_{j\beta}^{i\alpha} w^{j\beta}$$

Integrating over  $J$  (or equivalently setting  $s = 0$  in the effective equation for the generating function) one recovers the effective kinetics on slow states.

Expressions (147) and (148) involve quantities depending on the specific fast states ( $\pi_{j\beta}^{i\alpha}, \chi_{j\beta}^{i\alpha}$ ) and, hence, clearly show how it is impossible, in general, to express the effective evolution of a functional only in terms of functions of the states of the effective dynamics (in this case the blocks). However, this major short-coming can be overcome by considering that for such block-diagonal systems the only additional information required is the conditional probability of choosing a specific channel between blocks as depicted in Figure 21.

More specifically, we investigate the possibility of expressing the functional in terms of slow states and transitions only as

$$\mathcal{J}_{l,l'} \xrightarrow{\epsilon \rightarrow 0} \sum_{k=1}^{N+1} \int_{\tau_{k-1}}^{\tau_k} d\tau \bar{f}_{i_{k-1}} + \sum_{k=1}^N \bar{g}_{i_{k-1}}^{i_k} \quad (149)$$

with some suitable  $\bar{g}$  and  $\bar{f}$  depending on the block variables only. As shown in Ref. [22], a sufficient but obvious condition for a generic functional is that  $g_{j\beta}^{i\alpha} = g_j^i$  i.e., the transition dependent part does not depend on fast states.

In general, however, one has the effective equation for the generating function

$$\frac{dq_m^i}{dt} = \sum_j \bar{K}_j^i \exp(-s \bar{g}_j^i) q_m^j - \sum_k \bar{K}_i^k q_m^i + \sum_j C_j^i q_m^j \quad (150)$$

where the additional contribution features the matrix

$$C_j^i = \sum_{\alpha, \beta} S_{j\beta}^{i\alpha} w_{j\beta}^{\alpha} \left[ \exp(-s g_{j\beta}^{i\alpha}) - \exp(-s \bar{g}_j^i) \right] \quad (151)$$

which need not vanish. This means that on slow scales the effective evolution of the functional depends not only on the slow states and transitions but also on the specific fast states at which the slow transition took place. Consequently, for a correct description of generic functionals more details are needed than the ones available (and sufficient) from the effective evolution of the dynamics on the slow scales (see Fig. 21).

*Summary.* When fast transitions are block-diagonal, there are no decimated blocks. As a consequence, the only additional detail required to specify the evolution of a functional is which transition channel was chosen when a jump between two blocks took place.

#### 4.2.1. Counting statistics of transitions across blocks

An interesting functional to consider is the counting statistics of a single specified transition  $l\lambda \rightarrow n\nu$ , i.e.  $f = 0$  and  $\hat{g}_{j\beta}^{i\alpha} = \delta_{j\beta}^{l\lambda} \delta_{n\nu}^{i\alpha}$  one has  $\exp(-s \hat{g}_{j\beta}^{i\alpha}) = 1 + (\exp(-s) - 1) \delta_{j\beta}^{l\lambda} \delta_{n\nu}^{i\alpha}$  and the effective equation for the generating function in the limit  $\epsilon \rightarrow 0$  is

$$\frac{d\hat{q}_m^i}{dt} = \sum_j \bar{K}_j^i \left( \sum_{\alpha, \beta} \pi_{j\beta}^{i\alpha} \exp(-s \hat{g}_{j\beta}^{i\alpha}) \right) \hat{q}_m^j - \sum_j \bar{K}_i^j \hat{q}_m^j = \sum_j \bar{K}_j^i \hat{q}_m^j - \sum_j \bar{K}_i^j \hat{q}_m^j + \bar{K}_l^n (\exp(-s) - 1) \pi_{l\lambda}^{n\nu} \hat{q}_m^l \delta_n^i.$$

As expected, one needs to retain additional information about the fast states. In this case, simply knowing  $\pi_{l\lambda}^{n\nu}$ , i.e., the conditional probability of choosing the channel connecting state  $l\lambda$  to state  $n\nu$  once a transition between blocks  $l$  and  $n$  has occurred, is sufficient to provide the correct counting statistics in the limit  $\epsilon \rightarrow 0$ . For instance, the average effective transition rate  $n\nu \rightarrow l\lambda$  then follows from

$$\frac{d}{dt} \langle \#_{l\lambda}^{n\nu} \rangle = \frac{d}{dt} \sum_i \left( -\frac{d\hat{q}_m^i}{ds} \right)_{s=0} = \bar{K}_l^n \pi_{l\lambda}^{n\nu} \phi_m^l = S_{l\lambda}^{n\nu} w^{l\lambda} \phi_m^l$$

and the overall average transition rate  $l \rightarrow n$  is

$$\frac{d}{dt} \langle \#_l^n \rangle = \sum_{\lambda, \nu} S_{l\lambda}^{n\nu} w^{l\lambda} \phi_m^l = \bar{K}_l^n \phi_m^l$$

*Summary.* For block-diagonal fast transitions, the evolution of the counting statistics of transitions across blocks can be found if, in addition of the effective rates connecting the blocks, one has access to the probability of choosing a specific transition channel. Counting the transitions between blocks (irrespective of the specific states within the block) can be fully expressed in terms of the effective rates connecting the blocks of the effective dynamics.

#### 4.3. Entropy for block-diagonal dynamics

*The question.* Is it possible to express entropy production in terms of the rates and blocks describing the effective dynamics on the slow scale?

Another interesting functional of a stochastic trajectory is the entropy production. For its definition we shall introduce the concept of the time reversed trajectory, defined as

$$i^*(\tau) = i(t + t' - \tau)$$

where we note that the residence time spent in each state is the same as for the forward trajectory. The entropy production of a trajectory is then defined as the log-ratio of the probability of observing that forward trajectory  $\mathcal{P}$  compared to the backward one  $\mathcal{P}^*$  (see e.g. [9]):

$$S = \log \frac{\mathcal{P}}{\mathcal{P}^*} = -\log p_t^{i_t} + \log p_{t'}^{i_{t'}} + \mathcal{A}^* - \mathcal{A} = \underbrace{-\log p_t^{i_t} + \log p_{t'}^{i_{t'}}}_{\Delta S_p} + \underbrace{\sum_{k=1}^N \log \frac{K_{i_{k-1}}^{i_k}}{K_{i_k}^{i_{k-1}}}}_{S^{env}} \quad (152)$$

where  $p_t^i$  is the probability of starting in state  $i_t$  at the initial time  $t$  and  $\mathcal{A}$  is the action as defined in eq. (127).

The average rate of entropy production at time  $t$  can be written as

$$\langle \dot{S} \rangle = \sum_{i,j} p_i K_i^j \log \frac{p_i K_i^j}{p_j K_j^i}. \quad (153)$$

We see that the condition of detailed balance

$$p_i^{eq} K_i^j = p_j^{eq} K_j^i \quad (154)$$

corresponding to requiring that, at the steady state, each term of the sum in the master equation (3) vanishes, implies that the system is at equilibrium and that no entropy is produced. Furthermore, at detailed balance and at the steady state (equilibrium) there probability fluxes between states:

$$J_i^j = p_i K_i^j - p_j K_j^i \quad (155)$$

must be equal to zero.

Here we will derive the effective evolution of the entropy production on the slower scales as an illustration of the case for general functionals recovering the results of [22]. Let us first recall that also Ref. [14] considered the average entropy production of a system involving two time scales. The author showed that an entropy defined using only the effective rates would underestimate the effective entropy. Indeed, the effective entropy produced on the slower scales displayed a non-negative correction. The presence of the additional term was anticipated also in [18]. The authors of Ref. [17] showed that the effective entropy production satisfies an approximate fluctuation relation that becomes exact for infinite time-scale separation (as  $\epsilon \rightarrow 0$ ). Entropy for non block-diagonal fast dynamics was investigated in [16] that discussed the effect of decimation and in [92] which presented a different approach to decimation which ensured that the correct statistics of the dynamics and of its functionals are preserved.

We shall present here this issue for the complete generating function (hence not restricting to the average) within the framework for general functionals highlighted in the previous section. For the entropy production in the environment one has

$$S_{t,t'}^{env} = \sum_{k=1}^N \left(1 - \delta_{i_{k-1}}^{i_k}\right) \log \frac{S_{i_{k-1}\alpha_{k-1}}^{i_k\alpha_k}}{S_{i_k\alpha_k}^{i_{k-1}\alpha_{k-1}}} + \delta_{i_{k-1}}^{i_k} \log \frac{F_{i_{k-1}\alpha_{k-1}}^{i_k\alpha_k}}{F_{i_k\alpha_k}^{i_{k-1}\alpha_{k-1}}}$$

that can be rewritten as

$$S_{t,t'}^{env} = \log w^{i_t\alpha_t} - \log w^{i_{t'}\alpha_{t'}} + \underbrace{\sum_{k=1}^{N-1} \left(1 - \delta_{i_{k-1}}^{i_k}\right) \log \frac{S_{i_{k-1}\alpha_{k-1}}^{i_k\alpha_k} w^{i_{k-1}\alpha_{k-1}}}{S_{i_k\alpha_k}^{i_{k-1}\alpha_{k-1}} w^{i_k\alpha_k}} + \delta_{i_{k-1}}^{i_k} \log \frac{F_{i_{k-1}\alpha_{k-1}}^{i_k\alpha_k} w^{i_{k-1}\alpha_{k-1}}}{F_{i_k\alpha_k}^{i_{k-1}\alpha_{k-1}} w^{i_k\alpha_k}}}_{\mathcal{J}_{t,t'}}$$

As discussed before for generic functionals, the solvability condition at order  $\epsilon^{-1}$  requires  $g_{j\beta}^{i\alpha} = 0$ , which amounts to

$$\frac{F_{i\beta}^{i\alpha} w^{j\beta}}{F_{i\alpha}^{j\beta} w^{i\alpha}} = 1$$

i.e. detailed balance must hold for the fast processes. In this case

$$S_{t,t'}^{env} = \log w^{i_t\alpha_t} - \log w^{i_{t'}\alpha_{t'}} + \underbrace{\sum_{k=1}^{N-1} \left(1 - \delta_{i_{k-1}}^{i_k}\right) \log \frac{S_{i_{k-1}\alpha_{k-1}}^{i_k\alpha_k} w^{i_{k-1}\alpha_{k-1}}}{S_{i_k\alpha_k}^{i_{k-1}\alpha_{k-1}} w^{i_k\alpha_k}}}_{\mathcal{J}_{t,t'}}$$

so that we can identify

$$g_{j\beta}^{i\alpha} = \log \frac{S_{j\beta}^{i\alpha} w^{j\beta}}{S_{i\alpha}^{j\beta} w^{i\alpha}} \quad (156)$$

(where it is understood that  $g_{i\beta}^{i\alpha} = 0$ ). Notice that only transitions between slow states are counted as required by the solvability condition at order  $\epsilon^{-1}$ .

From the result of the general section we do not expect to be able to express the evolution of the effective functional in terms of only of the block variables and know that there should be an additional term as expressed in (151). To proceed to the study of such contribution we need to explicit the entropy production functional that one would define starting from the effective dynamics. This is given by

$$\mathcal{S}_{slow} = -\log \phi_i^{i_i} + \log \phi_{i'}^{i_{i'}} + \sum_{k=1}^N \log \frac{\bar{K}_{i_{k-1}}^{i_k}}{\bar{K}_{i_k}^{i_{k-1}}} \quad (157)$$

which obeys the fluctuation theorem (see Refs. [17, 22])

$$\langle e^{-\mathcal{S}_{slow}} \rangle = 1. \quad (158)$$

Then the related weight assigned to the slow transition reads

$$\bar{g}_j^i = \log \frac{\bar{K}_j^i}{\bar{K}_i^j} = -\log \left( \sum_{\alpha\beta} \pi_{j\beta}^{i\alpha} \exp(-g_{j\beta}^{i\alpha}) \right). \quad (159)$$

We can then read from eq. (151) the additional contribution:

$$\begin{aligned} C_j^i &= \sum_{\alpha\beta} S_{j\beta}^{i\alpha} w^{j\beta} [\exp(-s g_{j\beta}^{i\alpha}) - \exp(-s \bar{g}_j^i)] = \bar{K}_j^i \left[ \sum_{\alpha\beta} \pi_{j\beta}^{i\alpha} \left( \frac{S_{j\beta}^{i\alpha} w^{j\beta}}{S_{j\beta}^{i\alpha} w^{j\beta}} \right)^s - \left( \frac{\bar{K}_i^j}{\bar{K}_j^i} \right)^s \right] \\ &= \bar{K}_j^i \left( \frac{\bar{K}_i^j}{\bar{K}_j^i} \right)^s \left[ \sum_{\alpha\beta} \pi_{j\beta}^{i\alpha} \left( \frac{\pi_{j\beta}^{i\alpha}}{\pi_{j\beta}^{i\alpha}} \right)^s - 1 \right] \end{aligned}$$

Such additional contribution disappears (*i. e.*, it is possible to describe the effective evolution of the the functional in terms of the effective dynamics alone) if and only if

$$\frac{S_{j\beta}^{i\alpha} w^{j\beta}}{S_{i\alpha}^{j\beta} w^{i\alpha}} = \frac{\bar{K}_j^i}{\bar{K}_i^j} \quad (160)$$

*i.e.*

$$\pi_{j\beta}^{i\alpha} = \pi_{i\alpha}^{j\beta}. \quad (161)$$

A sufficient condition is that the full dynamics obeys detailed balance as shown also in [18]. Indeed, in this case

$$\frac{S_{j\beta}^{i\alpha}}{S_{i\alpha}^{j\beta}} = \frac{\rho^{i\alpha}}{\rho^{j\beta}} \quad (162)$$

where  $\rho$  is the equilibrium distribution for the full system. Then, in the limit  $\epsilon \rightarrow 0$

$$\frac{\rho^{i\alpha}}{\rho^{j\beta}} \rightarrow \frac{\varphi^i w^{i\alpha}}{\varphi^j w^{j\beta}} \quad (163)$$

where  $\varphi$  is the equilibrium distribution of the slow effective dynamics and therefore obeys

$$\frac{\bar{K}_j^i}{\bar{K}_i^j} = \frac{\varphi^i}{\varphi^j} \quad (164)$$



by detailed balance. Together with the two previous relations, this shows that the regularity condition (160) is satisfied. Therefore, at detailed balance, the limit of entropy production is regular and the effective Markov process with rates  $\bar{K}_j^i$  captures the correct entropy in addition to the correct kinetics.

Another sufficient condition is that there exists only one allowed transition between states  $j$  and  $i \neq j$  and back. In this case trivially  $\pi_j^i = \pi_i^j = 1$ , and the limit of the entropy production is regular as well.

Introducing the anomalous entropy production defined as the difference between the effective entropy production and the entropy defined from the effective dynamics equals:

$$\mathcal{S}_{anom} = \lim_{\epsilon \rightarrow 0} \mathcal{S} - \mathcal{S}_{slow} = \sum_{k=1}^N \log \frac{S_{i_k \alpha_k}^{i_k \alpha_k} w_{i_{k-1} \alpha_{k-1}}^{i_{k-1} \alpha_{k-1}} \bar{K}_{i_k}^{i_{k-1}}}{S_{i_k \alpha_k}^{i_{k-1} \alpha_{k-1}} w_{i_k \alpha_k}^{i_k \alpha_k} \bar{K}_{i_{k-1}}^{i_k}} = \sum_{k=1}^N \log \frac{\pi_{i_{k-1} \alpha_{k-1}}^{i_k \alpha_k}}{\pi_{i_k \alpha_k}^{i_{k-1} \alpha_{k-1}}} \quad (165)$$

It follows that

$$\exp[-\mathcal{S}_{anom}] = \frac{\prod_{k=1}^N \pi_{i_k \alpha_k}^{i_{k-1} \alpha_{k-1}}}{\prod_{k=1}^N \pi_{i_{k-1} \alpha_{k-1}}^{i_k \alpha_k}}$$

is the backward/forward ratio of conditional probabilities of fast states at a given sequence of slow states. The anomalous contribution, based on the probability of choosing transition channel once a transition between block has occurred, accounts for the possible cycles that where collapsed in the effective rates description.

The generating function of the anomalous entropy term obeys

$$\frac{d\tilde{q}_m^i}{dt} = \sum_j \bar{K}_j^i \tilde{q}_m^j - \sum_j \bar{K}_i^j \tilde{q}_m^j + \sum_j A_j^i \tilde{q}_m^j$$

which gives for  $s = 1$  (since  $A_j^i|_{s=1} = 0$ )

$$\langle e^{-\mathcal{S}_{anom}} \rangle = \sum_i \tilde{q}_m^i|_{s=1} = 1$$

and

$$\frac{d}{dt} \langle \mathcal{S}_{anom} \rangle = \sum_{i,j} \phi_m^j \bar{K}_j^i D\left(\pi_{j\beta}^{i\alpha} \parallel \pi_{i\alpha}^{j\beta}\right) \geq 0 \quad (166)$$

where  $D$  is the Kullback-Leibler divergence, one recovers the results of Ref. [14]. We have then seen how the effective dynamics may miss relevant parts of the entropy production thereby hiding some of the system irreversibility and dissipation. The authors of Ref. [42] showed that systems subject to fast drivings display a violation of the fluctuation-response relation and evaluated its typical shape in the space of frequencies for large time-scale separations. Such violation of the fluctuation response relation is known to be linked to entropy production for Langevin systems by the Harada-Sasa equality [93]. Investigating the connections between such violation of the fluctuation response relation in systems with time-scale separation and the anomalous entropy production represents an interesting future perspective.

*Summary.* When the original system does not obey detailed balance the entropy defined from the effective dynamics underestimates the full one. To recover the correct limit, it is necessary to include an additional contribution related to the different channels connecting the blocks. To compute the correct average entropy production it is sufficient to know what is the conditional probability of choosing a specific channel once a transition between two blocks has occurred.

#### 4.4. Some examples of coarse-graining of stochastic systems not based on time-scale separation

Before moving to some specific examples we shall briefly report on some studies that in a similar spirit to what we have shown here contrast the limiting behavior of coarse-grained functionals to the value they would take if defined from the coarse grained dynamics. In contrast to the main focus of the present report the coarse-graining considered in these studies does not rely on time-scale separation. In Ref. [94] the author considered how approximating a chemical master equation in terms of a diffusive process (either as a chemical Langevin equation [1] or as a system size expansion [25]) affects its entropy production. He showed that, away from equilibrium, the entropy production of

the diffusive approximations is unrelated to the original one of the chemical master equation. The authors of Ref. [95] considered the case of a colloidal probe attached to a molecular motor and derived a coarse grained description of the motor dynamics eliminating the probe. Such elimination involves continuous (probe position) and discrete (motor states) degrees of freedom and does not rely on a time-scale separation. In their study, a careful definition of the effective rates ensured the possibility to express the average entropy production in terms of the effective rates. Intuitively, this can be linked to the fact that there are no cycles in the full phase-space that are disrupted by the coarse-graining.

#### 4.5. Example for entropy production in discrete systems

##### 4.5.1. Irreversibility in two-component systems

Let us consider the thermodynamics of the biochemical sensing system described in section 2.3.2. We will show how, with the results of the previous section, we are able to derive the leading order contribution to the entropy production of the system when the receptor is much faster than the phosphorylation dynamics of the proteins and we shall compute its average value. Recall that since we are considering the case of a single receptor and no spontaneous (de-)phosphorylation, each transition between states of the Markov chain corresponds to a single chemical reaction. This ensures that the entropy production of the Markov chain (defined in 152) captures the ones produced in the chemical reactions [7]. The effective equation for the dynamics of the proteins derived in (47) satisfies detailed balance and, at the steady state, reaches equilibrium. This is not surprising since the reduced network is one-dimensional and cannot display cycles. Since the effective equation is at equilibrium, at the steady state, its associated entropy production is zero. However, we know from the initial dynamics that the full system is out of equilibrium and produces entropy. With the results from eq. (165) we can compute the statistics of this missing contribution without having to solve the full dynamics. The key idea is to retain information about the different channels connecting the effective slow states. We note in passing that, based on the observation that when concerning chemical systems one should account separately for the different chemical reaction connecting states of the Markov chain (see [7]), the authors of [41], in a model formally equivalent to the one considered here, exploited time separation to simplify the dynamics and derived the correct effective average entropy production. For the sake of illustration we shall compute the average entropy production of the system described in section 2.3.2. To evaluate the average anomaly we need to write the conditional probability of undergoing a specific transition between two fast states for a given slow transition:

$$\pi_{j\beta}^{i\alpha} = \frac{S_{j\beta}^{i\alpha} W^{j\beta}}{\bar{K}_j^i}. \quad (167)$$

As shown in figure 8 and in eq. (42) the only admissible transitions between slow states are the (de-)phosphorylation ones which connect states with the same receptor state

$$\begin{aligned} \pi_{x+1,ON}^{x,ON} &= \frac{p(ON)k_d^*}{\bar{K}_d} = \frac{p(ON)k_d^*}{p(ON)k_d^* + p(OFF)k_d} & \pi_{x,ON}^{x+1,ON} &= \frac{p(ON)k_p^*}{\bar{K}_p} = \frac{p(ON)k_p^*}{p(ON)k_p^* + p(OFF)k_p} \\ \pi_{x+1,OFF}^{x,OFF} &= \frac{p(OFF)k_d}{\bar{K}_d} = \frac{p(OFF)k_d}{p(ON)k_d^* + p(OFF)k_d} & \pi_{x,OFF}^{x+1,OFF} &= \frac{p(OFF)k_p}{\bar{K}_p} = \frac{p(OFF)k_p}{p(ON)k_p^* + p(OFF)k_p} \end{aligned} \quad (168)$$

We can now proceed to the evaluation of the average anomalous entropy production:

$$\frac{d}{dt} \langle S_{anom} \rangle = \sum_{x, x'} \phi_{x'} \bar{K}_{x'}^x \sum_{y, y'} \pi_{x', y'}^{x, y} \log \frac{\pi_{x', y'}^{x, y}}{\pi_{x, y}^{x', y'}}, \quad (169)$$

and carry out the sum over the slow states  $x'$  and  $y, y'$  which gives

$$\begin{aligned} \frac{d}{dt} \langle S_{anom} \rangle &= \sum_x \left[ (x+1) \phi_{x+1} \bar{K}_d \left( \frac{k_d p(OFF)}{\bar{K}_d} \log \frac{k_d \bar{K}_p}{k_p \bar{K}_d} + \frac{k_d^* p(ON)}{\bar{K}_d} \log \frac{k_d^* \bar{K}_p}{k_p^* \bar{K}_d} \right) \right. \\ &\quad \left. - (N-x) \phi_x \bar{K}_p \left( \frac{k_p p(OFF)}{\bar{K}_p} \log \frac{k_d \bar{K}_p}{k_p \bar{K}_d} + \frac{k_p^* p(ON)}{\bar{K}_p} \log \frac{k_d^* \bar{K}_p}{k_p^* \bar{K}_d} \right) \right]. \end{aligned} \quad (170)$$

The slow effective dynamics obeys detailed balance so that at the steady state for  $(x+1)\phi_{x+1}\bar{K}_d = (N-x)\bar{K}_p\phi_x$ . Exploiting this property and taking the sum over  $x$  one gets

$$\frac{d}{dt}\langle S_{anom} \rangle = N \frac{\bar{K}_p \bar{K}_d}{\bar{K}_p + \bar{K}_d} \left[ p(OFF) \left( \frac{k_d}{\bar{K}_d} - \frac{k_p}{\bar{K}_p} \right) \log \frac{k_d}{k_p} + p(ON) \left( \frac{k_d^*}{\bar{K}_d} - \frac{k_p^*}{\bar{K}_p} \right) \log \frac{k_d^*}{k_p^*} \right]. \quad (171)$$

By recalling the explicit expression of the effective rates one can rewrite the result as:

$$\frac{d}{dt}\langle S_{anom} \rangle = N \frac{\bar{K}_p \bar{K}_d}{\bar{K}_p + \bar{K}_d} \left[ p(ON) \left( \frac{k_d^*}{\bar{K}_d} - \frac{k_p^*}{\bar{K}_p} \right) \log \frac{k_d^* k_p}{k_p^* k_d} \right] \quad (172)$$

and finally obtain

$$\frac{d}{dt}\langle S_{anom} \rangle = N \frac{p(ON)p(OFF)}{\bar{K}_p + \bar{K}_d} \left[ (k_d^* k_p - k_p^* k_d) \log \frac{k_d^* k_p}{k_p^* k_d} \right]. \quad (173)$$

This result gives the entropy production up to corrections of order  $\epsilon$ . We remark that since the regular contribution to entropy vanishes in this case if we had defined the thermodynamics from the effective dynamics we would have obtained a vanishing entropy production overlooking the dissipation connected to the eliminated receptors' states. The only sets of parameters for which the computed entropy production vanishes are the ones where  $k_p^*/k_d^* = k_p/k_d$  which correspond to the detailed balance condition on the rates of the full system. At the steady state this implies that the full system is at equilibrium. This confirms the result we have obtained in the general case stating that if the full system obeys detailed balance there is no anomalous entropy production.

*Summary.* As we have seen before, two-components systems with fast receptor dynamics admit an effective kinetics in terms of the number of phosphorylated proteins only. The effective system, considering only the blocks (number of phosphorylated proteins), is apparently at equilibrium and therefore has a vanishing entropy production. The original system, however, does not obey detailed balance and at the steady state produces entropy with a finite rate. Such a rate can be correctly estimated if, in addition to the effective rates, one also has access to the probability that, given a phosphorylation event, the reaction involved an active or an inactive receptor.

## 5. The diffusive case

*The question.* We have seen under which conditions an effective diffusive dynamics can be derived for a diffusive system involving a fast and a slow scale. Is it possible to obtain an effective dynamics for a functional of the trajectories of the initial system? Can such effective evolution be expressed in terms of the effective dynamics derived in the previous section?

### 5.1. Averaging for functionals. Diffusive dynamics

We now focus on the study of functionals of the diffusive trajectory of a system involving two well separated time scales, described by Eqs. (81) and (82) that we report here for convenience

$$\begin{aligned} dX_t^i &= u^i(X_t, Y_t, t)dt + \beta^{ij}(X_t, Y_t, t) \cdot dB_t^j \\ dY_t^a &= \epsilon^{-1} z^a(X_t, Y_t, t)dt + \epsilon^{-1/2} \sigma^{ab}(X_t, Y_t, t) \cdot d\hat{B}_t^b \end{aligned}$$

Our interest is in eliminating the faster degrees of freedom and obtaining an effective description on the slower time scales as done for the dynamics. We will see that, as shown for the discrete case, it is not always possible to express the effective evolution of a functional solely as a functional of the effective dynamics but that additional details of the full process must be retained.

A possible way of approaching such problem is to perform the averaging procedure discussed for the dynamics in section 3 on the Feynman-Kac equation governing the evolution of the generating function of the functional of interest. Such approach would be similar to the one we have adopted for the discrete case and is the one followed,

for instance, in Ref. [21]. Here, we shall present an alternative method, generalizing the one exploited in Ref. [22]. Consider a general functional of the fast and slow processes:

$$Z = F(t, X_t, Y_t) - F(t', X_{t'}, Y_{t'}) + \underbrace{\int_{t'}^t h(\tau, X_\tau, Y_\tau) d\tau + r_i(\tau, X_\tau, Y_\tau) \cdot dX_\tau^i}_A + \underbrace{\int_{t'}^t f_a(\tau, X_\tau, Y_\tau) \cdot dY_\tau^a}_B \quad (174)$$

where all explicit time dependencies are  $O(1)$  and  $A$  evolves along the slow process  $X$  and  $B$  follows the fast one  $Y$ . Notice that this representation is not unique. For example, if  $f_a = \frac{\partial \phi}{\partial y^a}$  the  $B$  term can be removed by noticing that  $f_a \cdot dY^a = f_a \circ dY^a - \frac{1}{2} g^{ab} \frac{\partial f_a}{\partial y^b} d\tau = d\phi - \frac{\partial \phi}{\partial \tau} d\tau - \frac{\partial \phi}{\partial x^i} \circ dX^i - \frac{1}{2} g^{ab} \frac{\partial^2 \phi}{\partial y^a \partial y^b} d\tau$ . Therefore, in the following we shall assume that  $f_a$  has a rotational part only, i.e. it is an  $m$ -dimensional curl. We restrict to the case in which  $f$ ,  $r$  and  $h$  are of order 1. In general, they may have different scalings in powers of  $\epsilon$ , as in, for example, the large deviations study of Ref. [96].

The boundary terms statistics is, to lowest order, determined by the stationary distribution of the fast variables at given slow ones

$$\langle \delta(F(t, x, Y_t) - F_*) \rangle \xrightarrow{\epsilon \rightarrow 0} \int dy w(y) \delta(F(t, x, y) - F_*) \quad (175)$$

so that we can treat them separately. In other words, they become random variables whose distribution depends parametrically on the slow variables. The key idea of the present approach is to consider  $A$  and  $B$  as stochastic variables and study the generator of the joint process  $(X_t, A_t, Y_t, B_t)$ :

$$H = \underbrace{L_0 + (h + r_i u^i) \frac{\partial}{\partial A} + r_i d^{ij} \frac{\partial^2}{\partial A \partial x^j} + \frac{1}{2} d^{ij} r_i r_j \frac{\partial^2}{\partial A^2}}_{H_0} + \epsilon^{-1} \underbrace{\left[ M + f_a z^a \frac{\partial}{\partial B} + f_a g^{ab} \frac{\partial^2}{\partial B \partial y^b} + \frac{1}{2} f_a f_b g^{ab} \frac{\partial^2}{\partial B^2} \right]}_K \quad (176)$$

where  $L_0$  and  $M$  are the generators of the slow and fast dynamics as in eq. (81), (82). The intermediate steps are provided in appendix C. We can then address the problem of the averaging of the functional in terms of the adiabatic elimination of fast  $(Y_t, B_t)$  variables with slow  $(X_t, A_t)$  as done in section 3.

### 5.1.1. Stochastic integral at first order

Before proceeding, we notice that, at order  $\epsilon^{-1}$ , the problem admits a stationary solution only if  $f = 0$ , i.e. the stochastic integral can only have a gradient term depending on the fast trajectory. Indeed, for the process  $(Y_t, B_t)$  generated by  $K$ , at fixed slow variables, it follows from the existence of the equilibrium distribution of  $Y$  ( $w$ ) that at large times the marginal distribution of  $B$  at time  $t$  obeys a diffusion equation with constant drift  $\overline{f_a z^a}$  and diffusion  $\overline{f_a f_b g^{ab}}/2$ . Since the diffusion matrix of the fast process is positive, this implies that the stationary distribution can be obtained only if  $f = 0$ . With this requirement  $K = M$  and as in eq. (88):  $K^\dagger w = M^\dagger w = 0$ . Therefore

$$\left( \frac{\partial}{\partial \theta} + K \right) q^{(0)} = 0 \quad (177)$$

has a solution that is independent of the fast processes:

$$q^{(0)} = \eta(x, A, t) \quad (178)$$

At order  $\epsilon^0$

$$\left( \frac{\partial}{\partial t} + H_0 \right) q^{(0)} + \left( \frac{\partial}{\partial \theta} + K \right) q^{(1)} = 0 \quad (179)$$

admits a stationary solution only if it is orthogonal to the nullspace of  $M^\dagger$ , spanned by  $w$ . We then find

$$\left( \frac{\partial}{\partial t} + \overline{H}_0 \right) \eta = 0 \quad (180)$$

with the effective generator of the joint process  $(X, A)$  on slow scales:

$$\bar{H}_0 = \bar{L}_0 + \overline{(h + r_i u^i)} \frac{\partial}{\partial A} + \overline{r_i d^{ij}} \frac{\partial^2}{\partial A \partial x^j} + \frac{1}{2} \overline{d^{ij} r_i r_j} \frac{\partial^2}{\partial A^2} \quad (181)$$

where, as in section 3, the overbars denote averages over the equilibrium distribution of the fast process  $w(y)$ . We now convert the generator to the corresponding stochastic differential equations along slow trajectories for the variables  $X$ , following  $\bar{L}_0$  (just as in eq. 93) and  $A$  determined by the remaining terms. If there is no noise on the slow variables ( $d = 0$ ), the effective dynamics of eq. (93) is deterministic and the functional has the regular limit:  $dA_t = (\bar{h} + \overline{r_i u^i}) dt$ . If  $\bar{d} \neq 0$  the effective dynamics is diffusive and one has that the effective dynamics for  $A_t$  in the limit  $\epsilon \rightarrow 0$  is given by

$$dA_t = \left( \bar{h} + \overline{r_i u^i} - \bar{d}_{ik}^{-1} \overline{r_j d^{ij} u^k} \right) dt + \bar{d}_{ik}^{-1} \overline{r_j d^{ij}} \cdot dX_t^k + \left( \overline{d^{ij} r_i r_j} - \bar{d}_{ik}^{-1} \overline{r_j d^{ij}} \overline{r_l d^{kl}} \right)^{1/2} \cdot d\xi_t \quad (182)$$

along slow trajectories  $X_t$  generated by  $\bar{L}_0$ , where  $\xi_t$  is an independent Wiener process. The presence of the additional noise term implies that it is not possible to express the evolution of the statistics of the functional on the slow time scales in terms of the slow variables only. We remark that the term under the square root multiplying the noise is non-negative:

$$\overline{d^{ij} r_i r_j} \geq \bar{d}_{ik}^{-1} \overline{d^{ij} r_j} \overline{d^{kl} r_l}. \quad (183)$$

This follows from the non-negativity of the diffusion matrix of the slow variables  $d$ . Indeed,  $d^{ij}(v_i - r_i)(v_j - r_j) \geq 0$  for all vectors  $v$  implies  $\bar{d}^{ij} v_i v_j - 2 \overline{d^{ij} r_j} v_i + \overline{d^{ij} r_i r_j} \geq 0$  which in turn, for the specific choice  $v_i = \bar{d}_{ik}^{-1} \overline{d^{kl} r_l}$ , gives eq. (183) as required. The equality holds only when  $v_i = \bar{d}_{ik}^{-1} \overline{d^{kl} r_l} = r^i$ , i.e.  $r_i$  does not depend on  $y$ . Then, only when  $r$  is independent of the fast variables, it is possible to express the effective evolution of the functional as a stochastic integral over slow trajectories giving

$$\frac{\partial r_i}{\partial y_j} = 0, \forall i, j \quad \longrightarrow \quad dA_t = \bar{h} dt + r_k \cdot dX_t^k. \quad (184)$$

It is worth noticing that even in the case when neither  $u$  nor  $d$  depend on  $y$ , the dynamics of  $A$  will require the additional term if  $r$  depends on  $y$ . Indeed, in this case  $dA_t = \bar{h} dt + \bar{r}_k \cdot dX_t^k + \left[ d^{ij} (\bar{r}_i \bar{r}_j - \bar{r}_i \bar{r}_j) \right]^{1/2} \cdot d\xi_t$ . Also, when  $d$  is independent of  $y$  but  $u$  is not, one has  $dA_t = (\bar{h} + \overline{r_i u^i} - \bar{r}_i \bar{u}^i) dt + \bar{r}_k \cdot dX_t^k + \left[ d^{ij} (\bar{r}_i \bar{r}_j - \bar{r}_i \bar{r}_j) \right]^{1/2} \cdot d\xi_t$ .

### 5.1.2. Stochastic integral at order $\epsilon$

As we have seen for the dynamics in section 3, if  $\bar{u}^i = 0$  and  $d^{ij} = 0$  the slow dynamics will be on scales  $O(\epsilon)$ . The averaging of the functional becomes then more involved. First, for the dynamics of the functional to be on scales  $O(\epsilon)$  we need to require

$$\bar{h} + \overline{r_i u^i} = 0 \quad (185)$$

which gives

$$\frac{\partial \eta}{\partial t} = 0 \quad (186)$$

Under this condition, the solution is

$$q^{(1)} = - \left( M^{-1} u^i \right) \frac{\partial \eta}{\partial x^i} - \left( M^{-1} (h + r_i u^i) \right) \frac{\partial \eta}{\partial A} \quad (187)$$

apart from zero modes of  $M$ .

At order  $\epsilon$  one has

$$\left( \frac{\partial}{\partial \theta} + K \right) q^{(2)} = - \left( \frac{\partial}{\partial t} + H_0 \right) q^{(1)} - \frac{\partial}{\partial t} q^{(0)} \quad (188)$$

with solvability condition

$$\frac{\partial \eta}{\partial t} - \left( \frac{\partial}{\partial t} + u^i \frac{\partial}{\partial x^i} + (h + r_i u^i) \frac{\partial}{\partial A} \right) \left( (M^{-1} u^i) \frac{\partial}{\partial x^i} + (M^{-1} (h + r_i u^i)) \frac{\partial}{\partial A} \right) \eta = 0. \quad (189)$$

Making use of the commutativity condition (99) ensured by the detailed balance of the fast variables (see Appendix B.2 for the non-equilibrium case) and defining  $\alpha = h + r_k u^k$  we have

$$\begin{aligned} & \frac{\partial \eta}{\partial \tilde{t}} + U^i \frac{\partial \eta}{\partial \tilde{x}^i} + \frac{1}{2} D^{ij} \frac{\partial^2 \eta}{\partial \tilde{x}^i \partial \tilde{x}^j} + \\ & + \overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha} \frac{\partial \eta}{\partial A} + \overline{2\alpha (-M^{-1}) u^j} \frac{\partial^2 \eta}{\partial x^j \partial A} + \overline{\alpha (-M^{-1}) \alpha} \frac{\partial^2 \eta}{\partial A^2} = 0 \end{aligned} \quad (190)$$

where  $U$  and  $D$  are the drift and diffusion matrix of the effective dynamics as defined in eq. (98). Let us now compare this effective evolution with the one which can be defined in terms of the slow variables alone. If we require  $A_t$  to be expressed as a stochastic integral along slow trajectories  $\tilde{X}^i$  at order  $\epsilon$

$$d\tilde{X}_t^i = U^i dt + \zeta^{ij} \cdot dW_t^j \quad \tilde{A}_t = \int_r^t \tilde{h} d\tau + \tilde{f}_i \cdot d\tilde{X}^i \quad (191)$$

with

$$\zeta^{ik} \zeta^{jk} = D^{ij} \quad (192)$$

the process  $(\tilde{X}_t, \tilde{A}_t)$  is generated by

$$U^i \frac{\partial}{\partial \tilde{x}^i} + \frac{1}{2} D^{ij} \frac{\partial^2}{\partial \tilde{x}^i \partial \tilde{x}^j} + (\tilde{h} + \tilde{f}_i U^i) \frac{\partial}{\partial \tilde{A}} + \tilde{f}_i D^{ij} \frac{\partial^2}{\partial \tilde{x}^j \partial \tilde{A}} + \frac{1}{2} \tilde{f}_i \tilde{f}_j D^{ij} \frac{\partial^2}{\partial \tilde{A}^2} \quad (193)$$

If we want eq. (193) to be consistent with the result of the elimination of the fast variables (190) we need to impose

$$\tilde{f}_i = 2 \left( D^{-1} \right)_{ij} \overline{\alpha (-M^{-1}) u^j} \quad (194)$$

which consequently requires

$$2 \left( D^{-1} \right)_{ij} \overline{\alpha (-M^{-1}) u^j} \overline{\alpha (-M^{-1}) u^i} = -\overline{\alpha M^{-1} \alpha}. \quad (195)$$

If the latter equality is met, using the definition for  $\tilde{f}_i$  and the freedom in choosing  $\tilde{h}$ , a closed expression for  $A_t$  in terms of slow paths only can be obtained. As shown in appendix B.2.1, condition (195) is satisfied if and only if  $\alpha$  belongs to the subspace spanned by the vectors  $\{u_k, k = 1, \dots, n\}$ , or in other words,  $\alpha$  is a linear combination of the components of the slow drift  $u_k$  (i.e. with coefficients independent of the fast variables)<sup>10</sup> or, equivalently, must be amenable to the form

$$h = 0 \quad \text{and} \quad r_k \text{ depends on slow variables only.} \quad (196)$$

When  $\alpha$  is not a linear combination of the components of the slow drift  $u_k$  eq. (193) and (190) cannot be equal and it is then not possible to express the effective evolution of the functional only in terms of functions of the effective dynamics. To highlight the role played by the regular component of  $\alpha$  (parallel to  $u$ ) in the following we shall decompose  $\alpha$  as

$$\alpha = \alpha^\perp + \alpha^\parallel_j u^j \quad (197)$$

with  $\overline{\alpha^\perp M^{-1} u^j} = 0$  for all  $j$ , which gives

$$\tilde{f}_i = 2 \left( D^{-1} \right)_{ij} \overline{\alpha (-M^{-1}) u^j} = \left( D^{-1} \right)_{ij} \alpha^\parallel_k D^{jk} = \alpha^\parallel_i. \quad (198)$$

We remark that parallel and perpendicular have to be intended with respect to the product defined in (99). Making use of

$$M^{-1} \alpha = M^{-1} \alpha^\perp + \alpha^\parallel_k M^{-1} u^k \quad (199)$$

<sup>10</sup>Recall that the slow drift  $u$  depends in general on the fast variable  $y$  as shown in eq. (81).

and of the definitions of  $U$  and  $D$  given in eq. (98) we can express the effective equation for  $\eta$  (190) as

$$\begin{aligned} \frac{\partial \eta}{\partial t} + U^i \frac{\partial \eta}{\partial x^i} + \frac{1}{2} D^{ij} \frac{\partial^2 \eta}{\partial x^i \partial x^j} + \left( \overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} + \frac{1}{2} (D^{kj}) \frac{\partial \hat{\alpha}_k}{\partial x^j} + \alpha_k^\parallel U_k \right) \frac{\partial \eta}{\partial A} \\ + D^{jk} \alpha_k^\parallel \frac{\partial^2 \eta}{\partial x^j \partial A} + \frac{1}{2} D^{jk} \alpha_j^\parallel \alpha_k^\parallel \frac{\partial^2 \eta}{\partial A^2} + \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \frac{\partial^2 \eta}{\partial A^2} = 0 \end{aligned} \quad (200)$$

This corresponds to having that the functional  $A_t$  in the limit  $\epsilon \rightarrow 0$  becomes then a stochastic integral along slow trajectories plus an additional contribution

$$\lim_{\epsilon \rightarrow 0} A_t = \int_{t'}^t \alpha_k^\parallel \circ dX_\tau^k + \int_{t'}^t \overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} d\tau + \left( 2 \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \right)^{1/2} dW'_\tau \quad (201)$$

where  $W'_t$  is an independent Wiener process. Notice that, since  $\overline{u^i M^{-1} \alpha^\perp} = 0$  also  $\frac{\partial}{\partial x^i} \overline{u^i M^{-1} \alpha^\perp} = 0$  and we then have that

$$\overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} = - \left( \frac{\partial u^i}{\partial x^i} + u^i \frac{\partial \log w_{eq}}{\partial x^i} \right) (-M^{-1}) \alpha^\perp \quad (202)$$

which will prove important when discussing the averaging of entropy production (see [22]). To conclude we introduce the projection operator onto the subspace spanned by  $\{u_k, k = 1, \dots, n\}$ , defined as

$$\Pi(\bullet) = 2u^j (D^{-1})_{jk} \overline{\bullet (-M^{-1}) u^k} \quad (203)$$

which shall be useful for the discussion of specific examples. It follows that a generic  $\alpha = h + r_i u^i$  with  $\bar{\alpha} = 0$  can be decomposed in its parallel and perpendicular components by means of the projector:

$$h + r_i u^i = \underbrace{2 (D^{-1})_{jk} \overline{(h + r_i u^i) (-M^{-1}) u^k}}_{\alpha_j^\parallel} u^j + \underbrace{h + \left[ r_j - 2 (D^{-1})_{jk} \overline{(h + r_i u^i) (-M^{-1}) u^k} \right] u^j}_{\alpha^\perp}$$

*Summary.* It is possible to derive the effective evolution of a functional of the trajectories on the slow scales. However, in general, such functional cannot be written solely in terms of the effective trajectories.

## 5.2. Averaging of the entropy production of diffusive dynamics: the anomalous entropy

*The question.* Consider entropy production in the environment as a specific functional. Under what conditions can it be expressed in terms of the effective diffusion process? Which additional processes must be taken into consideration in order to recover the correct functional?

A functional of the stochastic trajectories that has attracted considerable attention is the entropy production [9, 97]. The averaging of entropy production for general diffusive processes was studied in detail in Ref. [22]. In general, the entropy production along a stochastic trajectory measures the irreversibility of a system and can be defined as the log ratio of the path probability forward and backward in time as shown in (152)

$$\mathcal{S}_{tot} \equiv \log \frac{\mathcal{P}}{\mathcal{P}^*}$$

and can be split as the sum of two contributions :

$$d\mathcal{S}_{tot} = d\mathcal{S}_p + \delta\mathcal{S}_{env} \quad (204)$$

where, the state function

$$\mathcal{S}_p(\mathbf{x}, \mathbf{y}, t) = -\ln p(\mathbf{x}, \mathbf{y}, t) \quad (205)$$

is defined as the logarithm of the probability density  $p$  at time  $t$  (the solution of the Fokker-Planck equation associated to Eq. (81)). For diffusive processes, the time-reversed process must be defined with additional care. For instance,

in the presence of dissipative forces (as for example friction) a naive inversion may lead to anti-dissipative dynamics (see Ref. [97] for detailed definitions, proofs and examples). To overcome this issue one should split the drift into a dissipative (+) and a conservative (−) part that transform as vector and pseudo vector fields under time-reversal

$$\begin{aligned} u &= u_+ + u_- & u_+ &\longrightarrow u_+ & u_- &\longrightarrow -u_- \\ z &= z_+ + z_- & z_+ &\longrightarrow z_+ & z_- &\longrightarrow -z_- \end{aligned}$$

For the study of entropy production on different time scales we shall consider the case in which the fast processes are completely dissipative, i.e. no conservative part of the drift  $z_- = 0$ . This is consistent with the requirement that the fast degrees of freedom are at equilibrium as required below. For a system obeying equations (81) and (82), the entropy produced in the environment for the full system of fast and slow variables reads

$$S_{env} = \int_{t'}^t 2g_{ab}^{-1} \hat{z}^b \circ dY_\tau^a + 2d_{ij}^{-1} \hat{u}_+^i \circ dX_\tau^j - 2d_{ij}^{-1} \hat{u}_+^i u_-^j d\tau - \frac{\partial u_-^i}{\partial x^i} d\tau \quad (206)$$

where  $\hat{z}^b = z^b - \frac{1}{2} \frac{\partial g^{ab}}{\partial y^a}$  and  $\hat{u}^i = u^i - \frac{1}{2} \frac{\partial d^{ij}}{\partial x^j}$ . As already discussed for the discrete case, in order to have a finite entropy production we must consider the case in which the fast degrees of freedom relax to an equilibrium steady-state  $w_{eq}$  as defined in eq. (88). By considering the Fokker-Planck equation associated to (82) one can see that requiring equilibrium corresponds to imposing

$$2g_{ab}^{-1} \hat{z}^b = \frac{\partial}{\partial y^a} \log w_{eq} \quad (207)$$

which ensures that the basic condition that  $f_a$  in eq. (174) be a gradient is met. This leads to the following expression

$$S_{env} = \log w_{eq}(X_t, Y_t, t) - \log w_{eq}(X_{t'}, Y_{t'}, t') + \quad (208)$$

$$+ \underbrace{\int_{t'}^t \left( \underbrace{2d_{ij}^{-1} \hat{u}_+^j - \frac{\partial \log w}{\partial x^i}}_{r_i} \cdot dX_\tau^i + \underbrace{\left( -\frac{\partial \log w}{\partial t} - \frac{1}{2} d^{ij} \frac{\partial^2 \log w}{\partial x^i \partial x^j} + d^{jk} \frac{\partial}{\partial x^k} (d_{ij}^{-1} \hat{u}_+^i) - 2d_{ij}^{-1} \hat{u}_+^i u_-^j - \frac{\partial u_-^i}{\partial x^i} \right)}_h d\tau \right)}_A \quad (209)$$

to which we can directly apply the results of the previous section.

#### Entropy at first order

Noticing that

$$\bar{\hat{u}}^i = \int w \left( u^i - \frac{1}{2} \frac{\partial d^{ij}}{\partial x^j} \right) dy = \bar{u}^i - \frac{1}{2} \frac{\partial \bar{d}^{ij}}{\partial x^j} + \frac{1}{2} \overline{d^{ij} \frac{\partial \log w}{\partial x^j}} = \hat{\bar{u}}^i + \frac{1}{2} \overline{d^{ij} \frac{\partial \log w}{\partial x^j}} \quad (210)$$

where we have introduced:

$$\hat{\bar{u}}^i = \bar{u}^i - \frac{1}{2} \frac{\partial \bar{d}^{ij}}{\partial x^j} . \quad (211)$$

Then, one has

$$\overline{d^{ij} r_j} = 2 \left( \bar{\hat{u}}_+^i - \frac{1}{2} \overline{d^{ij} \frac{\partial \log w}{\partial x^j}} \right) \equiv 2 \hat{\bar{u}}_+^i \quad (212)$$

$$\overline{d^{ij} r_i r_j} = 4 d_{ij}^{-1} \left( \hat{u}_+^i - \frac{1}{2} d^{ik} \frac{\partial \log w}{\partial x^k} \right) \left( \hat{u}_+^j - \frac{1}{2} d^{jl} \frac{\partial \log w}{\partial x^l} \right) = 4 \left( \overline{d_{ij}^{-1} \hat{u}_+^i \hat{u}_+^j} - \hat{u}_+^i \frac{\partial \log w}{\partial x^i} + \frac{1}{4} \overline{d^{ij} \frac{\partial \log w}{\partial x^i} \frac{\partial \log w}{\partial x^j}} \right) \quad (213)$$

and finally, making use of  $\overline{\partial_t \log w} = 0$  the asymptotic slow dynamics

$$dA_t = \underbrace{2 \bar{d}_{ij}^{-1} \hat{\bar{u}}_+^i \circ dX_\tau^j - 2 \bar{d}_{ij}^{-1} \hat{\bar{u}}_+^i \bar{u}_-^j d\tau - \frac{\partial \bar{u}_-^i}{\partial x^i} d\tau}_{dS_{env}^{slow}} + dS_{anom} \quad (214)$$



along slow trajectories  $X_t$  generated by  $\bar{L}_0$ . The first term coincides with the definition of entropy one would have starting from the effective diffusive dynamics of eq. (92). The additional anomalous contribution reads

$$dS_{anom} = \frac{1}{2}l d\tau + l^{1/2}d\xi_t \quad (215)$$

where  $l$  is defined as

$$l = 4 \left( d_{ij}^{-1} \left( \hat{u}_+^i - \frac{1}{2} d^{ik} \frac{\partial \log w}{\partial x^k} \right) \left( \hat{u}_+^j - \frac{1}{2} d^{jl} \frac{\partial \log w}{\partial x^l} \right) - \bar{d}_{ij}^{-1} \hat{u}_+^i \hat{u}_+^j \right) \geq 0 \quad (216)$$

and  $\xi_t$  is yet another independent Wiener process. Interestingly, it can be shown that

$$\langle e^{-S_{anom}} \rangle = 1. \quad (217)$$

If the full system is at equilibrium, the anomalous contribution can be shown to vanish.

#### Entropy at order $\epsilon$

As seen for the general functional, in case  $\bar{u}^i = 0$  and  $d^{ij} = 0$  the solution is to be sought at order  $\epsilon$ . In such case, the slow dynamics is deterministic and this implies that the slow drift will be conservative:  $u_+ = 0$  (see [97]).

This simplifies the expression of (206) to

$$S_{env} = \int_{t'}^t 2g_{ab}^{-1} \hat{z}^b \circ dY_\tau^a - \frac{\partial u^i}{\partial x^i} d\tau \quad (218)$$

which, exploiting the equilibrium condition on fast variables (207) and rearranging the terms can be expressed as

$$S_{env} = \log w_{eq}(X_t, Y_t, t) - \log w_{eq}(X_{t'}, Y_{t'}, t') - \underbrace{\int_{t'}^t w_{eq}^{-1} \frac{\partial}{\partial x^i} (u^i w_{eq}) d\tau}_{A_t} \quad (219)$$

under the assumption that  $w_{eq}$  depends on  $O(\epsilon)$  times only. We can now make use of the results of the previous section. Identifying  $\alpha = w_{eq}^{-1} \frac{\partial}{\partial x^i} (u^i w_{eq})$  and applying the projector defined in eq. (203) we can obtain the component parallel to the drift

$$\Pi \left( w_{eq}^{-1} \frac{\partial}{\partial x^i} (u^i w_{eq}) \right) = 2u^j (D^{-1})_{jk} \overline{w_{eq}^{-1} \left( \frac{\partial}{\partial x^i} (u^i w_{eq}) \right) (-M^{-1}) u^k} = 2u^j (D^{-1})_{jk} \left( \frac{1}{2} \frac{\partial D^{ik}}{\partial x^i} - U^k \right) \quad (220)$$

$$= -2 \underbrace{(D^{-1})_{jk} \hat{U}^k u^j}_{\alpha_j^\parallel} \quad (221)$$

and the regular part of the entropy in the limit  $\epsilon \rightarrow 0$  is

$$S_{reg}^{\epsilon \rightarrow 0} = \int_{t'}^t 2 (D^{-1})_{jk} \hat{U}^k \circ dX_\tau^j \quad (222)$$

As for the additional contribution one has

$$\overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} = -\overline{w_{eq}^{-1} \left( \frac{\partial}{\partial x^i} (u^i w_{eq}) \right) (-M^{-1}) \alpha^\perp} = \overline{\alpha (-M^{-1}) \alpha^\perp} = \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \quad (223)$$

and

$$dS_{anom} = \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} d\tau + \left( 2\overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \right)^{1/2} dW_t' \quad (224)$$

which implies for the averages along trajectories and  $W_t'$

$$d\langle S_{anom} \rangle \geq 0 \quad (225)$$

and

$$d\langle e^{-S_{anom}} \rangle = -\langle e^{-S_{anom}} dS_{anom} \rangle + \langle \alpha^\perp (-M^{-1}) \alpha^\perp e^{-S_{anom}} \rangle dt = 0 \quad (226)$$

with

$$\alpha^\perp = -w_{eq}^{-1} \frac{\partial}{\partial x^i} (u^i w_{eq}) - 2 (D^{-1})_{jk} \hat{U}^k u^j. \quad (227)$$

*Summary.* We derived under what conditions on the system drift and diffusion coefficient the limit of the entropy production of the full system coincides with the one of the effective system. When such conditions are not met, an anomalous entropy production is present. It is positive on average and to describe its evolution it is necessary to introduce an additional independent white-noise term.

### 5.3. Examples for functionals of diffusive trajectories

#### 5.3.1. Adaptation in microevolution

Let us now consider an example where the elimination procedure stops at order  $\epsilon^0$ . As we have seen in section 3.2.1 the effective equation for the evolution of a genotype in a rapidly fluctuating environment that does not favor on average any genotype seems to be neutral (see eq. 108).

We have seen in eq. (101) that the global fitness of a population in a varying environment changes accordingly with positive contributions given by adaptation and negative ones due to the unsteadiness of the environment. We can now consider it more in detail and write

$$dF(X_t, Y_t) = \underbrace{s(X_t, Y_t) \circ dX_t}_{\text{adaptation}} + \underbrace{\frac{\partial F}{\partial y} \circ dY_t}_{\text{env. changes}} \quad (228)$$

where  $X_t$  and  $Y_t$  are, respectively, the first genotype frequency and the environmental state at time  $t$ . The first term on the right hand side accounts for the changes in fitness caused by changes in the genotype frequencies. It is the fitness flux at time  $t$  introduced in Ref.[74]

$$d\phi(t) = s(X_t, Y_t) \circ dX_t = \frac{\partial F}{\partial x} \circ dX_t. \quad (229)$$

It provides a measure of the adaptation driven by natural selection in the spirit of Fisher's derivation of his fundamental theorem (see [98] for a general discussion). Intuitively, this can be understood by taking the case in which the first genotype has a higher fitness; *i. e.*, positive selection coefficient  $s > 0$ . When the first genotype increases its frequency, the population is adapting to the environment and this gives a positive fitness flux.

Generally speaking, the process of adaptation to an environment during the course of time is not time symmetric. It shows a temporal direction and is therefore an irreversible process. A precise connection between population genetics and out-of-equilibrium, irreversible stochastic systems can be made (see e.g. Ref. [99, 74]). With the general results of the previous section we can investigate whether the limit of the fitness flux coincides with the one defined from the effective slow dynamics (in which case it should vanish). We find that, despite the fact that the genotype follows a neutral effective evolution, adaptation is continuously taking place yielding a non-zero fitness flux. Such result was obtained in Ref. [83] to which we refer for a step by step derivation. By use of eq. (182), identifying  $r = s(x, y)$ ,  $h = 0$ , and recalling that  $u = s(x, y)x(1 - x) + m(x)$  and that the diffusion coefficient of the slow system  $d = x(1 - x)/N$  does not depend on the fast variables we have

$$\lim_{\epsilon \rightarrow 0} d\phi_t = \left[ (\bar{s}^2 - \bar{s} \bar{s}) x(1 - x)/N \right] dt + \bar{s} \cdot dX_t + \left( (\bar{s}^2 - \bar{s} \bar{s}) x(1 - x)/N \right)^{1/2} \cdot d\xi_t \quad (230)$$

As a consequence, in the microevolutionary limit the average value of the fitness flux is always greater than what one would obtain by simply using the definition (229) with the effective dynamics. In order to understand the implications of this result, consider the case in which the average selection vanishes *i.e.* no specific genotype is favored in the long term. In this case, the effective Kimura-Ohta equation is not subject to natural selection and we would expect no adaptation as, for example shown in eq. (108). However, if we compute the limiting value of fitness flux we obtain

a finite positive value testifying that adaptation is continuously taking place. This is what happens for example if the environment follows an Ornstein-Uhlenbeck process discussed in section 3.2.1 where  $\bar{s} = 0$  and  $\overline{s^2} = \sigma^2 D/K$ . At the stationary state, the regular term of the fitness flux  $\langle \phi_{eff} \rangle$  is equal to zero because  $\bar{s} = 0$  and the anomalous one gives

$$\lim_{\epsilon \rightarrow 0} \langle d\phi(t) \rangle = \langle d\phi_{anom} \rangle = \frac{D}{K} \sigma^2 \langle g \rangle \langle x(1-x) \rangle / N \quad (231)$$

which is positive on average. Let us interpret such result. The population is evolving in a rapidly fluctuating environment and consequently it is subject to an erratic selection so that, if one studies the evolution of the population on long time scales it may seem neutral because the random contributions of the selection exerted by the succession of environments tend to cancel off. However, this apparent neutrality does not mean that the population has not been subject to selection and that it has not adapted to the environments it has encountered. Indeed, despite the fast environmental switches, the population manages to adapt on the fast time scales yielding a finite positive contribution to the fitness which is given by eq. (231).

*Summary.* We considered the evolution of a population under the influence of a rapidly changing stochastic environment. On a slow scale, the population dynamics is set by the average selection exerted by the environment. However, if one measures how much the population has adapted to the environment one finds an additional positive contribution to what would be estimated from the effective dynamics alone. Most notably, for an environment that is on average neutral, one finds a finite rate of adaptation.

### 5.3.2. Thermodynamics of a Brownian particle in a temperature gradient

As we have discussed in section 3.2.2 an example of a multiscale continuous system with effective dynamics at the order  $\epsilon$  is the Langevin-Kramers dynamics in the strong friction limit which describes the Brownian motion of a particle immersed in a fluid with temperature  $T$ . We study here the averaging of entropy production of a Brownian particle in a temperature gradient. We cast the results of [21] within the framework of the general procedure for the homogenization of stochastic functionals provided in section 5.1. For Langevin-Kramers dynamics the entropy produced by the particle in the environment (the fluid) along a path is given by the integral of the released heat divided by temperature

$$\mathcal{S}_{env} = \int_{t'}^t \left( \frac{f^i(X_\tau, \tau) V_\tau^i}{T(X_\tau, \tau)} d\tau - \frac{V_\tau^i}{T(X_\tau, \tau)} \circ dV_\tau^i \right). \quad (232)$$

as detailed in Refs. [9, 10, 97]

The equations describing the process are (110) and, for the sake of compactness we do not consider the external force ( $f = 0$ ) and we restrict to a constant friction coefficient. In the formalism of equations (81) and (82) we have that the slow drift  $u^i = V_t^i$  and that there is no noise on the slow variable.

We recall that the fast drift  $z^a = -\gamma v^a$  is given by the friction term and the diffusion matrix for the fast variables is  $g^{ab} = 2T\gamma\delta^{ab}$ . With these choices, we have that the eigenfunctions of  $M$  are the Hermite polynomials (see 115) and the equilibrium distribution corresponds to the local Maxwellian (see 114). Since there is no noise on the slow variable and the slow drift has zero average with respect to the equilibrium distribution,  $\bar{L} = 0$  and the effective dynamics takes place on time scales of order  $\epsilon$ . According to the definition of equation (98) the effective drift is the  $U = 0$  and the diffusion matrix  $D^{ij} = \frac{T}{\gamma}\delta^{ij}$ . When temperature does not depend on space, we see from (232) that the integral can be performed immediately and we are left with boundary terms only:  $\mathcal{S}_{env} = (V_{t'}^2 - V_t^2)/2T$ . In this case then  $\alpha = 0$ . On the contrary, if temperature does depend on space we can rewrite:

$$\mathcal{S}_{env} = \frac{V_{t'}^j V_{t'}^j}{T(X_{t'})} - \frac{V_t^j V_t^j}{T(X_t)} - \int_{t'}^t \frac{\partial T(X_\tau)}{\partial x^i} \frac{V_\tau^i}{2T^2(X_\tau)} V_\tau^j V_\tau^j d\tau \quad (233)$$

where we have made use of the fact that  $dX^i = V^i dt$ . We then have that

$$\alpha = -\frac{\partial T}{\partial x^i} \frac{v^i}{2T^2} v^j v^j. \quad (234)$$

We can split it into two components, a part parallel (with respect to the product defined in (99)) to the drift of the slow variables  $u^i = v^i$  and an orthogonal one. Recalling that for this generator we have that the Hermite polynomials are eigenfunctions

$$M(\underbrace{v^i}_{H_1}) = -\gamma \underbrace{v^i}_{H_1} \quad M(\underbrace{v^i(v^j v^j - (n+2)T)}_{H_3}) = -3\gamma \underbrace{v^i(v^j v^j - (n+2)T)}_{H_3} \quad (235)$$

and provide an orthogonal base:

$$\int (v^i(v^j v^j - (n+2)T)) v^i w(y) dy = \int H_3 H_1 w(y) dy = 0, \quad (236)$$

we can then decompose

$$\alpha = -\frac{\partial T}{\partial x^i} \frac{1}{2T^2} (H_3 + (n+2)T H_1) \quad (237)$$

where the component parallel to the drift reads:

$$\alpha^{\parallel i} v^j = -\frac{\partial T}{\partial x^i} \frac{(n+2)}{2T} v^j \quad (238)$$

and the orthogonal one gives

$$\alpha^\perp = \frac{\partial T}{\partial x^i} \frac{v^i}{2T^2} ((n+2)T - v^j v^j). \quad (239)$$

Hence, the regular part of the entropy production reads

$$\mathcal{S}_{reg}^{\epsilon \rightarrow 0} = - \int_{t'}^t \frac{(n+2)}{2T} \frac{\partial T}{\partial x^i} \circ dX_\tau^j \quad (240)$$

and the anomalous contribution is given by

$$d\mathcal{S}_{anom} = \frac{\partial T}{\partial x^i} \frac{\partial T}{\partial x^i} \frac{(n+2)}{6\gamma T} d\tau + \left( \frac{\partial T}{\partial x^i} \frac{\partial T}{\partial x^i} \frac{(n+2)}{3\gamma T} \right)^{1/2} dW'_\tau. \quad (241)$$

Notice that the fact that

$$\overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} = \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \quad (242)$$

is not accidental but completely general for the averaging of entropy production (see eq. 223 and [22]). Finally, by separating the boundary terms  $nd \log T$  that will combine with the other boundary terms  $d(v^2/T)$  to give the Maxwellian, one recovers the results of Ref. [21]. The presence of the positive correction to the average entropy production was also identified in [100]. Some recent studies have extended the analysis of the anomalous entropy to the rotational degrees of freedom of the brownian particle [23, 24].

The symmetry breaking in the velocity distribution introduced by the presence of temperature gradients is responsible for the presence of the anomaly and may affect also other functionals. In the following we shall consider some other thermodynamic functionals and systematically compare the *exact asymptotic* expression for vanishing inertia to the overdamped *approximation*. We will see that some of them are sensitive to these effects (which are neglected by the overdamped approximation) and will therefore pick up anomalous contributions whereas others are not affected by such corrections and will be simply given by the corresponding definition in the overdamped approximation.

*Heat.* The case of the heat exchange between a Brownian particle and the environment in presence of a temperature gradient was considered in Ref. [101]. When the thermal environment is inhomogeneous it is important to consider separately the heat exchanges that take place at different temperatures. It is then useful to define the average rate of heat release to the thermostat at a specific temperature. As shown in the supplementary material of [101] the asymptotic expressions for the heat released at a given temperature in the limit of vanishingly small inertia is not regular. This is at the core of the entropic anomaly.

On the contrary, the overall heat exchange (irrespective of the thermostat) has a regular behaviour, its definition coincides with the one given for the overdamped effective dynamics as shown also in Ref. [102].

*Excess and housekeeping entropy.* The excess entropy is the contribution to entropy production due to unsteadiness of the environment through time-changes of protocol, temperature, friction, etc. It measures the additional dissipation due to external driving modifying the non-equilibrium steady state. If such driving takes place on slow time scales the limit is then regular. The regularity of excess entropy upon elimination of variables in the form of insensitivity to coarse graining has been discussed in Refs. [19, 20]. The anomalous entropy therefore contributes to the housekeeping entropy which is the contribution to entropy production due to the maintenance of an out-of-equilibrium state. In conclusion the limit of the housekeeping entropy is anomalous.

*Summary.* Consider diffusion in a fluid subject to a temperature gradient. For large friction (small inertia) the dynamics can be described in terms of the positional degrees of freedom alone (overdamped approximation), averaging over velocities. The rate of entropy production in the environment in the overdamped approximation underestimates the actual contribution. The missing dissipation is linked to the fact that the overdamped system assumes a symmetric velocity distribution whereas the full system does not have this symmetry, even in the limit of vanishing inertia. The anomalous entropy production takes its name from this irreversibility linked to the asymmetries that are overlooked by the overdamped approximation.

#### 5.4. Homogenization and information loss

*The question.* Is it possible to give an interpretation of the entropic anomaly in terms of information loss?

Intuitively, averaging over some degrees of freedom and reducing the amount of details used in the description of a system is linked to information loss. Such intuition can be substantiated by considering our analysis on the averaging of functionals of the stochastic trajectories. The study of entropy production offers a rather transparent interpretation in terms of information theory and the anomalous contributions missed by the effective dynamics can be directly linked to missing information.

By its very definition entropy production has an informational meaning and can be seen as the log-likelihood of the forward process versus the backward one (see eq. 152). As such, it can be employed to test the hypothesis that the process is the forward one versus the one that it is the backward one *i.e.* to test the direction of the arrow of time [103, 104]. Then, the average entropy production is the Kullback-Leibler divergence between the forward and the backward process:

$$D_{KL}(\mathcal{P}||\mathcal{P}^*) \equiv \langle \mathcal{S}(x) \rangle. \quad (243)$$

It can be interpreted in terms of the expected discrimination information between the forward and backward evolution hypotheses. Indeed, according to the Stein lemma, the Kullback-Leibler divergence sets the rate at which the probability of a false negative decision (type II error) exponentially decreases with repeated measurements [105, 106]. The Kullback-Leibler divergence, similarly to mutual information, obeys a data processing inequality [107, 106] so that, loosely speaking, acting on the original variables (here a trajectory), will not increase the divergence of the two probabilities. We can consider the averaging procedure presented in the previous sections as the transformation we are applying to our variables: a projection from the set of complete paths to the space of the effective paths. Then, according to the data processing inequality, the difference between the Kullback-Leibler divergence of the full process and the one of the effective dynamics must be non negative and, in the limit of large time scales separation, defines the average anomalous entropy production

$$\lim_{\epsilon \rightarrow 0} D_{KL}(\mathcal{P}||\mathcal{P}^*) - D_{KL}(\mathcal{P}_{eff}||\mathcal{P}_{eff}^*) = \langle \mathcal{S}_{anom}(x) \rangle \geq 0. \quad (244)$$

Then one sees how the average anomalous entropy production quantifies the loss in the ability to discriminate the forward and backward trajectory when the comparison is carried out by means of the projected effective dynamics instead of the full one. An interesting corollary of the data processing inequality is that the Kullback-Leibler of the projected process is equal to the original one only in case the effective dynamics is a sufficient statistic for the direction of the arrow of time. We know that the anomalous entropy production vanishes when the rates obey detailed balance. This means that, in this case, the trajectories of the effective system contain as much information on the time irreversibility of the system as the original ones.

An interesting question to address in the future is to consider the influence of the averaging procedure on the ability to discriminate between dynamics transformation that are not just time reversal but related to different symmetries such as rotations or general isometries, as the ones considered in [108, 109].

Additionally, as shown in Ref. [104], the steady state average entropy production rate can be shown to be inversely proportional to the minimal time needed to decide on the direction of the arrow of time. In this framework, missing some entropy production implies needing longer observation times before being able to decide if the system is evolving forward in time. The average anomalous entropy production represents how much more time one needs to wait if one has access only to the effective dynamics of the system.

*Summary.* The entropy that is missed by the effective dynamics (anomaly) can be interpreted as a loss in the ability of discriminating the direction of the arrow of time.

## 6. Conclusion and discussion

In the present report we have considered stochastic systems involving well separated time scales. The existence of such time-scale separation motivates and justifies the attempt to derive effective dynamics taking place on the slower time scales resulting from decimation and coarse-graining of the faster processes. The reduced effective process usually involves fewer degrees of freedom (varying on the slower time scales) and is, consequently, more amenable to analytical treatments and numerical simulation. We focused on continuous-time discrete-state and diffusive Markov processes and used a systematic averaging procedure to obtain the effective dynamics. Such procedure allowed us to highlight what are the conditions under which the averaged dynamics are Markovian and to what extent the original system can be simplified. With the same tools we addressed the behavior of functionals of the stochastic trajectory upon averaging the faster processes. Our central attention was devoted to the question: is it possible to express the effective evolution of a generic functional on the slower time scales as a functional of the reduced effective dynamics? We have found that under general conditions this is not possible. In other words, the effective description of a functional requires more details than the ones sufficient to describe the dynamics. We have studied what are the necessary additional details that must be retained to provide a consistent representation of the functional and shown how to account for them in the effective description.

The first message that we intend to convey takes the form of a warning. Often, one studies a system starting with equations that result from the elimination of some faster degrees of freedom but are capable of capturing the relevant features of the dynamics taking place at the chosen scale. Our findings suggest that additional care must be taken when studying functionals. Such issue is best captured by the example of entropy production, a measure of irreversibility. For such functional, the eliminated variables, though having no impact on the dynamics, are crucial to characterize irreversibility and hence entropy production. An effective dynamics that apparently seems at equilibrium may, in fact, hide some underlying nonequilibrium processes that give rise to a finite entropy production and dissipation.

On the other hand, we have highlighted what are the additional details that are needed for a consistent description on the slow scales, for general functionals and for entropy production in particular. In this perspective our results provide a tool for deriving the correct effective descriptions without the necessity of studying the full system involving fast and slow processes. We have provided an application of such method to give the effective dynamics of the counting statistics of a given transition for a discrete Markov process and to correctly compute the entropy production of stochastic systems. The applicability of these general results have been illustrated by specific examples ranging from the entropy production of a Brownian particle in an inhomogeneous temperature environment to the effective thermodynamics of simple biochemical network involving fast and slow reactions and to measures of adaptation in a model of population genetics in a rapidly changing environment.

In summary, the elimination of fast transitions is a procedure that can be in general performed in stochastic systems, to some degree. Due attention must be paid to the fact that some information about fast processes must be retained. Asymptotic methods allow to identify this information and provide a way to derive effective equations and develop efficient algorithms that correctly describe both dynamics and functionals of trajectories on slow time-scales.

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### A. Quasi equilibrium Michaelis-Menten with low substrate abundance.

Let us consider the case of a Michaelis-Menten enzymatic reaction at low substrate concentration where we allow reversible product formation. This is an extension of the model discussed in section 2.3.3.



where the  $k$  are the specific probability rate constants, i.e. the rates for single molecule reactions. The system is in a state specified by the number of free enzymes  $e$ , substrate molecules  $s$ , enzyme-substrate complexes  $c$ , and products  $d$ . However, the conservation laws impose

$$e + c = e_n \quad s + c + d = m$$

where the total number of enzymes (free or in complex)  $e_n$  and the  $m$  are fixed by the initial state.

Choosing  $d$  and  $c$  as independent state variables, taking values in the ranges  $0 \leq c \leq \min(m, e_n)$  and  $0 \leq d + c \leq m$ , the master equation reads

$$\begin{aligned} \frac{d}{dt}p(c, d) = & k_1(e_n - c + 1)(m - d - c + 1)p(c - 1, d) - k_1(e_n - c)(m - d - c)p(c, d) + k_{-1}(c + 1)p(c + 1, d) - k_{-1}cp(c, d) \\ & + k_2(c + 1)p(c + 1, d - 1) - k_2cp(c, d) + k_{-2}(e_n - c + 1)(d + 1)p(c - 1, d + 1) - k_{-2}(e_n - c)d p(c, d) \end{aligned}$$

or, in compact form

$$\frac{d}{dt}P^{cd} = \sum_{c'd'} K_{c'd'}^{cd} P^{c'd'} - K_{cd}^{c'd'} P^{cd}$$

with

$$K_{c'd'}^{cd} = k_1(e_n - c')(m - d' - c')\delta_{c'}^{c-1}\delta_{d'}^d + k_{-1}c'\delta_{c'}^{c+1}\delta_{d'}^d + k_2c'\delta_{c'}^{c+1}\delta_{d'}^{d-1} + k_{-2}(e_n - c')d'\delta_{c'}^{c-1}\delta_{d'}^{d+1}$$

Let us consider the quasi equilibrium case: i. e., the reactions that involve the product are far slower than the other ones. In this case

$$K_{c'd'}^{cd} = \epsilon^{-1} F_{c'd'}^{cd} \delta_{d'}^d + S_{c'd'}^{cd} (1 - \delta_{d'}^d)$$

where

$$\epsilon^{-1} F_{c'd}^{cd} = k_1(e_n - c')(m - d - c')\delta_{c'}^{c-1} + k_{-1}c'\delta_{c'}^{c+1} \quad S_{c'd'}^{cd} = k_2c'\delta_{c'}^{c+1}\delta_{d'}^{d-1} + k_{-2}(e_n - c')d'\delta_{c'}^{c-1}\delta_{d'}^{d+1}$$

In this case, the transition matrix of the fast dynamics is block diagonal and we can use the results of section 2.2. In the limit  $\epsilon \rightarrow 0$ , the slow states, labeled by  $d$ , evolve according to the effective Markov process

$$\frac{d}{dt}P^d = \sum_{c'd'} \bar{K}_{d'}^d P^{d'} - \bar{K}_d^{d'} P^d$$

where, according to eq. 29,

$$\bar{K}_{d'}^d = \sum_{c,c'} S_{c'd'}^{cd} w^{c'd'}$$

and  $w^{c'd'}$  is the steady state of the fast dynamics at fixed  $d'$ , i.e. the solution of

$$k_1(e_n - c + 1)(m - d - c + 1)w^{c-1,d} - k_1(e_n - c)(m - d - c)w^{c,d} + k_{-1}(c + 1)w^{c+1,d} - k_{-1}cw^{c,d} = 0$$

If detailed balance holds for the fast system, then the equilibrium solution has to obey

$$\left( k_1(e_n - c')(m - d - c')\delta_{c'}^{c-1} + k_{-1}c'\delta_{c'}^{c+1} \right) w_{eq}^{c'd} = \left( k_1(e_n - c)(m - d - c)\delta_c^{c'-1} + k_{-1}c\delta_c^{c'+1} \right) w_{eq}^{cd}$$

i.e.

$$k_1(e_n - c + 1)(m - d - c + 1)w_{eq}^{c-1,d} = k_{-1}cw_{eq}^{cd}$$

which is easily solved to give

$$w_{eq}^{cd} = w_{e_n m}^{0d} \left( \frac{k_1}{k_{-1}} \right)^c \frac{e_n!(m-d)!}{(e_n-c)!(m-d-c)!c!}$$

The constant is found by imposing normalization

$$\frac{1}{w_{e_n m}^{0d}} = \sum_{c=0}^{\min(e_n, m-d)} \left( \frac{k_1}{k_{-1}} \right)^c \frac{e_n!(m-d)!}{(e_n-c)!(m-d-c)!c!}$$

One has therefore

$$\begin{aligned} \bar{K}_{d'}^d &= w_{e_n m}^{0d'} \sum_{c=0}^{\min(e_n, m-d)} \sum_{c'=0}^{\min(e_n, m-d')} \left( k_2 c' \delta_{c'}^{c+1} \delta_{d'}^{d-1} + k_{-2} (e_n - c') d' \delta_{c'}^{c-1} \delta_{d'}^{d+1} \right) \left( \frac{k_1}{k_{-1}} \right)^{c'} \frac{e_n!(m-d')!}{(e_n-c')!(m-d'-c')!c'!} \\ &= k_2 w_{e_n m}^{0d'} \delta_{d'}^{d-1} \sum_{c=0}^{\min(e_n, m-d)} \sum_{c'=0}^{\min(e_n, m-d')} c' \delta_{c'}^{c+1} \left( \frac{k_1}{k_{-1}} \right)^{c'} \frac{e_n!(m-d')!}{(e_n-c')!(m-d'-c')!c'!} \\ &\quad + k_{-2} w_{e_n m}^{0d'} \delta_{d'}^{d+1} \sum_{c=0}^{\min(e_n, m-d)} \sum_{c'=0}^{\min(e_n, m-d')} (e_n - c') d' \delta_{c'}^{c-1} \left( \frac{k_1}{k_{-1}} \right)^{c'} \frac{e_n!(m-d')!}{(e_n-c')!(m-d'-c')!c'!} \\ &= k_2 w_{e_n m}^{0d'} \delta_{d'}^{d-1} \left( \frac{k_1}{k_{-1}} \right) e_n(m-d') \sum_{c'=1}^{\min(e_n, m-d')} \left( \frac{k_1}{k_{-1}} \right)^{c'-1} \frac{(e_n-1)!(m-d'-1)!}{(e_n-1-(c'-1))!(m-d'-1-(c'-1))!(c'-1)!} \\ &\quad + k_{-2} w_{e_n m}^{0d'} \delta_{d'}^{d+1} e_n d' \sum_{c'=0}^{\min(e_n-1, m-d')} \left( \frac{k_1}{k_{-1}} \right)^{c'} \frac{(e_n-1)!(m-d')!}{(e_n-c'-1)!(m-d'-c')!c'!} \end{aligned}$$

Renominating  $c' - 1 \rightarrow c'$  in the first sum, using  $\min(e_n, m-d') - 1 = \min(e_n - 1, m - 1 - d')$  and resumming one obtains

$$\bar{K}_{d'}^d = k_2 e_n(m-d') \left( \frac{k_1}{k_{-1}} \right) \frac{w_{e_n m}^{0d'}}{w_{e_n-1, m-1}^{0d'}} \delta_{d'}^{d-1} + k_{-2} e_n d' \frac{w_{e_n m}^{0d'}}{w_{e_n-1, m}^{0d'}} \delta_{d'}^{d+1}$$

Notice that the effective rate can also be written as

$$\bar{K}_{d'}^d = k_2 \langle c | e_n m d' \rangle_{eq} \delta_{d'}^{d-1} + k_{-2} d' (e_n - \langle c | e_n m d' \rangle_{eq}) \delta_{d'}^{d+1}$$

where

$$\langle c | e_n m d' \rangle_{eq} = \sum_{c=0}^{\min(e_n, m-d)} c w_{eq}^{cd}$$

#### A.1. Thermodynamics of quasi equilibrium Michaelis-Menten

As we have seen in section 4.3, in the case of block-diagonal fast dynamics the additional anomalous entropy to the one expressed in terms of the effective rates involves the conditional probabilities

$$\pi_{c'd'}^{cd} = \frac{S_{c'd'}^{cd} w_{c'd'}^{c'd'}}{\bar{K}_{d'}^d} = \delta_{d'}^{d-1} \delta_{c'}^{c+1} \frac{c' w_{e_n m}^{c'd'}}{\langle c | e_n m d' \rangle_{eq}} + \delta_{d'}^{d+1} \delta_{c'}^{c-1} \frac{(e_n - c') w_{e_n m}^{c'd'}}{e_n - \langle c | e_n m d' \rangle_{eq}}$$

The only pair that survives in the present case is

$$\begin{aligned} \pi_{c+1, d-1}^{cd} &= \frac{(c+1) w_{e_n m}^{c+1, d-1}}{\langle c | e_n, m, d-1 \rangle_{eq}} \\ \pi_{cd}^{c+1, d-1} &= \frac{(e_n - c) w_{e_n m}^{c, d}}{e_n - \langle c | e_n, m, d \rangle_{eq}} \end{aligned}$$

However, since the complete system obeys detailed balance, we know from section 4.3 that there will be no anomalous entropy production.



### A.1.1. Single enzyme Michaelis-Menten

For a single enzyme ( $e_n = 1$ ) it is simple to evaluate the fast equilibrium probabilities:

$$w_{eq}^{cd} = \begin{cases} \frac{1}{\left(1+(m-d)\frac{k_1}{k_{-1}}\right)} & \text{for } c = 0 \\ \frac{(m-d)\frac{k_1}{k_{-1}}}{\left(1+(m-d)\frac{k_1}{k_{-1}}\right)} & \text{for } c = 1 \end{cases}$$

$$\langle c|1md\rangle_{eq} = \frac{(m-d)}{\left(\frac{k_{-1}}{k_1} + (m-d)\right)}$$

and the effective rate from substrate to product:

$$\bar{K}_d^{d+1} = k_2 \langle c|1md\rangle_{eq} = \frac{k_2(m-d)}{\left(\frac{k_{-1}}{k_1} + (m-d)\right)}$$

which is equivalent to the rate appearing in macroscopic chemical kinetics and in eq. (61). In this case, the conditional probability of choosing a specific channel for going from substrate to product are trivial since it is possible to form a product only from the state with one complex  $c = 1$

$$\pi_{1,d-1}^{0d} = \frac{w_{eq}^{1,d-1}}{\langle c|1,m,d-1\rangle_{eq}} = 1$$

and the reverse one

$$\pi_{0d}^{1,d-1} = \frac{w_{eq}^{0,d}}{1 - \langle c|1,m,d\rangle_{eq}} = 1.$$

We then clearly see that, as proven in general for systems obeying detailed balance, there is no anomalous entropy production.

### A.1.2. Two enzymes Michaelis-Menten

When  $e_n = 2$

$$w_{eq}^{cd} = \begin{cases} \frac{1}{\left(1+2(m-d)\frac{k_1}{k_{-1}}+(m-d)(m-d-1)\left(\frac{k_1}{k_{-1}}\right)^2\right)} & \text{for } c = 0 \\ \frac{2(m-d)\frac{k_1}{k_{-1}}}{\left(1+2(m-d)\frac{k_1}{k_{-1}}+(m-d)(m-d-1)\left(\frac{k_1}{k_{-1}}\right)^2\right)} & \text{for } c = 1 \\ \frac{(m-d)(m-d-1)\left(\frac{k_1}{k_{-1}}\right)^2}{\left(1+2(m-d)\frac{k_1}{k_{-1}}+(m-d)(m-d-1)\left(\frac{k_1}{k_{-1}}\right)^2\right)} & \text{for } c = 2 \end{cases}$$

and the average number of complexes reads:

$$\langle c|2md\rangle_{eq} = 2(m-d)\left(\frac{k_1}{k_{-1}}\right) \frac{1 + (m-d-1)\left(\frac{k_1}{k_{-1}}\right)}{\left(1 + 2(m-d)\frac{k_1}{k_{-1}} + (m-d)(m-d-1)\left(\frac{k_1}{k_{-1}}\right)^2\right)}.$$

The effective rate of product formation is obtained by  $k_2 \langle c|2md\rangle_{eq}$ . One can see that it reduces to the macroscopic Michaelis-Menten equilibrium approximation in the case of large substrate abundance which grants that  $m-d \simeq m-d-1$ . The conditional probability for different transition channels read:

$$\pi_{1,d-1}^{0d} = \frac{w_{2m}^{1,d-1}}{\langle c|2,m,d-1\rangle_{eq}} = \frac{1}{1 + (m-d)\left(\frac{k_1}{k_{-1}}\right)}$$

$$\begin{aligned}\pi_{2,d-1}^{1d} &= \frac{2w_{2m}^{2,d-1}}{\langle c|2, m, d-1\rangle_{eq}} = \frac{(m-d)\left(\frac{k_1}{k-1}\right)}{1 + (m-d)\left(\frac{k_1}{k-1}\right)} \\ \pi_{0d}^{1,d-1} &= \frac{2w_{2m}^{0,d}}{2 - \langle c|2, m, d\rangle_{eq}} = \frac{1}{1 + (m-d)\left(\frac{k_1}{k-1}\right)} \\ \pi_{1d}^{2,d-1} &= \frac{w_{2m}^{1,d}}{2 - \langle c|2, m, d\rangle_{eq}} = \frac{(m-d)\left(\frac{k_1}{k-1}\right)}{1 + (m-d)\left(\frac{k_1}{k-1}\right)}\end{aligned}$$

showing that, as expected from the detailed balance condition, there is no anomalous entropy production.

## B. Proofs for the effective dynamics of diffusive systems at order $\epsilon$ and extensions to non-equilibrium fast diffusive processes

We here provide the proof that  $\overline{M^{-1}f} = 0$  for any  $f$  such that  $\bar{f} = 0$ . We also show that when the fast dynamics reaches an equilibrium steady state, eq. (99) holds: *i. e.*, for any  $f$  and  $g$  with  $\bar{f} = \bar{g} = 0$  we have that  $\overline{g(-M^{-1}f)} = \overline{f(-M^{-1}g)}$ . We start by considering fast dynamics that reaches a steady state on the short time scales characterized by a steady state distribution  $w(y)$  which is not necessarily an equilibrium one. For any  $\bar{f} = 0$ , one can write for a generic variable  $y$

$$f(y') = \int dy \delta(y - y') f(y) - \underbrace{\int dy w(y) f(y)}_{=0}$$

which can be expressed in terms of the propagator  $W$  of the fast process generated by  $M$  by recalling that

$$W(y, t|y', t) = \delta(y - y') \quad w(y) = W(y, t|y', -\infty)$$

so that

$$f(y') = \int dy \left[ \int_{-\infty}^t dt' \frac{\partial}{\partial t'} W(y, t|y', t') \right] f(y). \quad (\text{B.1})$$

The fast propagator obeys

$$\left( \frac{\partial}{\partial t'} + M' \right) W(y, t|y', t') = 0 \quad \left( \frac{\partial}{\partial t} - M^\dagger \right) W(y, t|y', t') = 0 \quad (\text{B.2})$$

and admits a biorthogonal decomposition as

$$\begin{aligned}W(y, t|y', t') &= \sum_E \phi_E(y') \phi_E^+(y) e^{-E(t-t')} \\ M\phi_E &= -E\phi_E \quad M^\dagger \phi_E^+ = -E\phi_E^+.\end{aligned} \quad (\text{B.3})$$

In general, combining this expression with eq. (B.1) we have that

$$f(y') = - \int dy \int_{-\infty}^t dt' [M' W(y, t|y', t')] f(y)$$

and that consequently

$$\begin{aligned}(-M^{-1}f)(y') &= \int dy \int_{-\infty}^t dt' W(y, t|y', t') f(y) = \\ &= \int dy \int_{-\infty}^t dt' \sum_E \phi_E(y') \phi_E^+(y) e^{-E(t-t')} f(y) = \\ &= \left( \sum_{E>0} E^{-1} \phi_E(y') \int dy \phi_E^+(y) f(y) \right) + \phi_0(y') \int_{-\infty}^t dt' \bar{f} = \\ &= \sum_{E>0} E^{-1} \phi_E(y') \int dy \phi_E^+(y) f(y).\end{aligned} \quad (\text{B.4})$$

Since the steady state is the right eigenfunction associate with the 0 eigenvalue ( $w = \phi_0^+$ ) it is orthogonal to the eigenfunctions spanning the other eigenspaces and we finally obtain:

$$\overline{M^{-1}f} = 0. \quad (\text{B.5})$$

With eq. (B.4) we can express the effective diffusion coefficient appearing in eq. (98), as

$$D^{ij} = 2\overline{u^i(-M^{-1}u^j)} = 2\sum_{E>0} E^{-1} \int dz' \phi_E(z') w(z') u^i(z') \int dz \phi_E^+(z) u^j(z) = 2\sum_{E>0} E^{-1} \overline{\phi_E u^i} \int dz \phi_E^+(z) u^j(z) \quad (\text{B.6})$$

This also implies the Green-Kubo-Taylor formula for the diffusion coefficient

$$\frac{1}{2}D^{ij} = -\overline{u^i(M^{-1}u^j)} = \int dy dz \int_{-\infty}^t dt' w(y) u^i(y, t) W(z, t|y, t') u^j(z, t) = \int_{-\infty}^t dt' \langle u^i(X_t, Y_t, t) u^j(X_{t'}, Y_{t'}, t) \rangle_{ss, fast} \quad (\text{B.7})$$

We remark that for non-equilibrium fast dynamics, the diffusion matrix in general is not symmetric. It can however, be shown to be positive definite by proving that

$$\overline{f(-M^{-1})f} > 0 \quad (\text{B.8})$$

for any function  $f$  satisfying  $\overline{f} = 0$ . Since the process is stationary the autocorrelation depends only on the difference between the times  $\tau = t - t'$  and we can express the product

$$\overline{f(-M^{-1})f} = \int_0^\infty d\tau \langle f^i(X_t, Y_t, \tau) f^j(X_t, Y_0, 0) \rangle_{ss, fast}$$

The Wiener Kinchin theorem states that

$$\langle \hat{f}(k) \hat{f}^*(q) \rangle = \frac{1}{2\pi} \delta(k - q) \int_{-\infty}^\infty d\tau \langle f(\tau) f(0) \rangle e^{ik\tau}$$

where  $\hat{f}(k)$  denotes the Fourier transform. By setting  $q = k = 0$  we have

$$\frac{1}{\pi} \overline{f(-M^{-1})f} = \frac{1}{\pi} \int_0^\infty d\tau \langle f^i(X_t, Y_t, \tau) f^j(X_t, Y_0, 0) \rangle = \langle |\hat{f}(0)|^2 \rangle \geq 0$$

that proves (B.8) for all functions such that  $\hat{f}(0) = \int_{-\infty}^\infty d\tau f(\tau) \neq 0$ .

The asymmetry of the diffusion matrix (B.6) is not relevant for the propagator since the it is traced with the space derivatives. We can therefore define a symmetrized diffusion matrix without altering the form of propagator:

$$\tilde{D}^{ij} = \left( \frac{D^{ij} + D^{ji}}{2} \right) = \overline{u^i(-M^{-1}u^j)} + \overline{u^j(-M^{-1}u^i)} \quad (\text{B.9})$$

where clearly  $D^{ij} \frac{\partial^2 \rho}{\partial x^i \partial x^j} = \tilde{D}^{ij} \frac{\partial^2 \rho}{\partial x^i \partial x^j}$ .

### B.1. Equilibrium dynamics

If the steady state of the fast variable is an equilibrium one

$$\phi_E^+ = w_{eq} \phi_E \quad (\text{B.10})$$

by detailed balance and, by use of equation (B.4) one has that, for any  $f$  and  $g$  with  $\overline{f} = \overline{g} = 0$

$$\overline{g(-M^{-1}f)} = \sum_{E>0} E^{-1} \overline{f \phi_E} \overline{g \phi_E} = \overline{f(-M^{-1}g)} \quad (\text{B.11})$$

The diffusion coefficient is therefore symmetric and positive

$$\frac{1}{2}D^{ij} = \overline{u^i(-M^{-1}u^j)} = \sum_{E>0} E^{-1} \overline{\phi_E u^i} \overline{\phi_E u^j} \quad (\text{B.12})$$

### B.2. Functionals for non-equilibrium fast dynamics

In this appendix we generalize the discussion of section 5.1.2 to the case in which the fast dynamics reach a non-equilibrium steady state. The main difference is that in the non-equilibrium case is that, at variance with (99), in general,

$$\overline{g(-M^{-1}f)} \neq \overline{f(-M^{-1}g)} \quad (\text{B.13})$$

which implies that eq. (190) becomes

$$\begin{aligned} & \frac{\partial \eta}{\partial \tilde{t}} + U^i \frac{\partial \eta}{\partial x^i} + \frac{1}{2} D^{ij} \frac{\partial^2 \eta}{\partial x^i \partial x^j} + \\ & + u^i \frac{\partial}{\partial x^i} \overline{(-M^{-1})\alpha} \frac{\partial \eta}{\partial A} + \left( \overline{\alpha(-M^{-1})u^j} + \overline{u^j(-M^{-1})\alpha} \right) \frac{\partial^2 \eta}{\partial x^j \partial A} + \overline{\alpha(-M^{-1})\alpha} \frac{\partial^2 \eta}{\partial A^2} = 0 \end{aligned} \quad (\text{B.14})$$

If we want eq. (193) to be consistent with the result of the elimination of the fast variables (B.14) we need to impose

$$\tilde{f}_i = (D^{-1})_{ij} \left( \overline{\alpha(-M^{-1})u^j} + \overline{u^j(-M^{-1})\alpha} \right) \quad (\text{B.15})$$

which consequently requires

$$\frac{1}{2} (D^{-1})_{ij} \left( \overline{\alpha(-M^{-1})u^j} + \overline{u^j(-M^{-1})\alpha} \right) \left( \overline{\alpha(-M^{-1})u^i} + \overline{u^i(-M^{-1})\alpha} \right) = -\overline{\alpha M^{-1} \alpha} \quad (\text{B.16})$$

If the latter equality is met, using the definition for  $\tilde{f}_i$  and the freedom in choosing  $\tilde{h}$ , a closed expression for  $A_t$  in terms of slow paths only can be obtained.

#### B.2.1. Conditions for the regularity of a functional of a diffusive trajectory.

We show here that condition (B.16) is satisfied if and only if  $\alpha$  belongs to the subspace spanned by the vectors  $\{u_k, k = 1, \dots, n\}$ . The same steps can be applied to the simpler case of equilibrium fast dynamics and condition (195)

Defining  $\beta_i = (\zeta^{-1})_{ij} u^j$  equation (B.16) takes the form

$$\left( \overline{\alpha(-M^{-1})\beta_k} + \overline{\beta_k(-M^{-1})\alpha} \right) \left( \overline{\alpha(-M^{-1})\beta_k} + \overline{\beta_k(-M^{-1})\alpha} \right) = -2\overline{\alpha M^{-1} \alpha} \quad (\text{B.17})$$

This means that  $\alpha$  must be in the subspace spanned by the vectors  $\{\beta_k, k = 1, \dots, n\}$ , or in other words,  $\alpha$  is a linear combination of the functions  $\beta_k$  (i.e. with coefficients independent of the fast variables). Indeed, noticing that

$$-\overline{\beta_k(M^{-1}\beta_l)} - \overline{\beta_l(M^{-1}\beta_k)} = (\zeta^{-1})_{ik} D^{ij} (\zeta^{-1})_{jl} = \delta_{kl} \quad (\text{B.18})$$

and decomposing  $\alpha$  in components within the subspace and orthogonal to it

$$\alpha = \alpha^\perp + \tilde{\alpha}_i \beta_i \quad \text{where} \quad -\overline{\alpha^\perp M^{-1} \beta_j} - \overline{\beta_j M^{-1} \alpha^\perp} = 0 \quad \text{for all } j = 1, \dots, n \quad (\text{B.19})$$

we have

$$\overline{\alpha^\perp(-M^{-1})\alpha^\perp} = \sum_{E>0} E^{-1} \overline{\alpha^\perp \phi_E} \int \alpha^\perp(z) \phi_E^+(z) dz = 0 \quad (\text{B.20})$$

which, given (B.8), implies  $\alpha^\perp = 0$  (the component along  $\phi_0$  is absent since  $\overline{\alpha^\perp} = 0$ ).

### B.2.2. Corrections to the regular terms

When  $\alpha$  is not a linear combination of the components of the slow drift  $u_k$  eq. (193) and (190) cannot be equal and it is then not possible to express the effective evolution of the functional only in terms of functions of the effective dynamics. To highlight the role played by the regular component of  $\alpha$  (parallel to  $u$ ) in the following we shall decompose  $\alpha$  as

$$\alpha = \alpha^\perp + \alpha^\parallel_j u^j \quad (\text{B.21})$$

with  $\overline{\alpha^\perp M^{-1} u^j} = 0$  for all  $j$ , which gives

$$\tilde{f}_i = 2 \left( D^{-1} \right)_{ij} \overline{\alpha(-M^{-1} u^j)} = \left( D^{-1} \right)_{ij} \alpha^\parallel_k D^{jk} = \alpha^\parallel_i. \quad (\text{B.22})$$

Making use of

$$M^{-1} \alpha = M^{-1} \alpha^\perp + \alpha^\parallel_k M^{-1} u^k \quad (\text{B.23})$$

and of the definitions of  $U$  and  $D$  given in eq. (98) we can express the effective equation for  $\eta$  (190) as

$$\begin{aligned} \frac{\partial \eta}{\partial \tilde{t}} + U^i \frac{\partial \eta}{\partial x^i} + \frac{1}{2} D^{ij} \frac{\partial^2 \eta}{\partial x^i \partial x^j} + \left( \overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} + \frac{1}{2} \left( D^{kj} + \overline{u^j M^{-1} u^k} - \overline{u^k M^{-1} u^j} \right) \frac{\partial \alpha^\parallel_k}{\partial x^j} + \alpha^\parallel_k U_k \right) \frac{\partial \eta}{\partial A} \\ + D^{jk} \alpha^\parallel_k \frac{\partial^2 \eta}{\partial x^j \partial A} + \frac{1}{2} D^{jk} \alpha^\parallel_j \alpha^\parallel_k \frac{\partial^2 \eta}{\partial A^2} + \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \frac{\partial^2 \eta}{\partial A^2} = 0 \end{aligned} \quad (\text{B.24})$$

This corresponds to having that the functional  $A_t$  in the limit  $\epsilon \rightarrow 0$  becomes then a stochastic integral along slow trajectories plus an additional contribution

$$\lim_{\epsilon \rightarrow 0} A_t = \int_{t'}^t \alpha^\parallel_k \circ dX_\tau^k + \int_{t'}^t \left[ \overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} + \frac{1}{2} \left( \overline{u^j M^{-1} u^k} - \overline{u^k M^{-1} u^j} \right) \frac{\partial \alpha^\parallel_k}{\partial x^j} \right] d\tau + \left( 2 \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \right)^{1/2} dW'_\tau \quad (\text{B.25})$$

In case

$$\frac{\partial \alpha^\parallel_i}{\partial x^j} = \frac{\partial \alpha^\parallel_j}{\partial x^i} \quad (\text{B.26})$$

which corresponds to an irrotational  $\alpha^\parallel$  then (B.25) simplifies to

$$\lim_{\epsilon \rightarrow 0} A_t = \int_{t'}^t \alpha^\parallel_k \circ dX_\tau^k + \int_{t'}^t \overline{u^i \frac{\partial}{\partial x^i} (-M^{-1}) \alpha^\perp} d\tau + \left( 2 \overline{\alpha^\perp (-M^{-1}) \alpha^\perp} \right)^{1/2} dW'_\tau \quad (\text{B.27})$$

where  $W'_t$  is an independent Wiener process.

We then introduce the projection operator onto the subspace spanned by  $\{u_k, k = 1, \dots, n\}$ , defined as

$$\Pi(\bullet) = u^j \left( D^{-1} \right)_{jk} \left( \overline{\bullet (-M^{-1}) u^k} + \overline{u^k (-M^{-1}) \bullet} \right) \quad (\text{B.28})$$

It follows that a generic  $\alpha = h + r_i u^i$  with  $\overline{\alpha} = 0$  can be decomposed in its parallel and perpendicular components by means of the projector:

$$\begin{aligned} h + r_i u^i &= \underbrace{\left( D^{-1} \right)_{jk} \left( \overline{(h + r_i u^i) (-M^{-1}) u^k} + \overline{u^k (-M^{-1}) (h + r_i u^i)} \right)}_{\alpha^\parallel_j} u^j + \\ &+ \underbrace{h + \left[ r_j - \left( D^{-1} \right)_{jk} \left( \overline{(h + r_i u^i) (-M^{-1}) u^k} + \overline{u^k (-M^{-1}) (h + r_i u^i)} \right) \right]}_{\alpha^\perp} u^j \end{aligned} \quad (\text{B.29})$$

### C. Generator of a joint stochastic process.

To illustrate the steps required to obtain eq. (176), in this appendix we show how to derive the generator of the joint process  $X_t, Y_t, \mathcal{A}_t$  following equations (81), (82) and (174) i.e.

$$dX_t^i = u^i(X_t, Y_t, t)dt + \beta^{ij}(X_t, Y_t, t) \cdot dB_t^j \quad (C.1)$$

$$dY_t^a = \epsilon^{-1} z^a(X_t, Y_t, t)dt + \epsilon^{-1/2} \sigma^{ab}(X_t, Y_t, t) \cdot d\hat{B}_t^b \quad (C.2)$$

$$d\mathcal{A}_t = r_i(X_t, Y_t, t) \cdot dX_t^i + h dt \quad (C.3)$$

where as before

$$d^{ij} = \beta^{ik} \beta^{jk} \quad g^{ab} = \sigma^{ac} \sigma^{bc}. \quad (C.4)$$

The case with an additional functional  $B$  of the fast variables is analogous. Similarly to the derivation of Itô's formula we express the differential of a generic function  $f(X_t, Y_t, \mathcal{A}_t)$  as

$$df = \left[ dX^i \frac{\partial}{\partial x^i} + \frac{1}{2} dX^i dX^j \frac{\partial^2}{\partial x^i \partial x^j} + dY^a \frac{\partial}{\partial y^a} + \frac{1}{2} dY^a dY^b \frac{\partial^2}{\partial y^a \partial y^b} + d\mathcal{A} \frac{\partial}{\partial A} + \frac{1}{2} d\mathcal{A}^2 \frac{\partial^2}{\partial A^2} + dX^i dY^a \frac{\partial^2}{\partial x^i \partial y^a} + d\mathcal{A} dX^i \frac{\partial^2}{\partial A \partial x^i} + d\mathcal{A} dY^a \frac{\partial^2}{\partial A \partial y^a} \right] f \quad (C.5)$$

so that upon taking the average and retaining only the contributions of order  $O(dt)$  we have that

$$\frac{d\langle f \rangle}{dt} = \left\langle \underbrace{\left[ u^i \frac{\partial}{\partial x^i} + \frac{1}{2} d^{ij} \frac{\partial^2}{\partial x^i \partial x^j} \right]}_{L_0} + \underbrace{\left[ \epsilon^{-1} z^a \frac{\partial}{\partial y^a} + \epsilon^{-1} \frac{1}{2} g^{ab} \frac{\partial^2}{\partial y^a \partial y^b} \right]}_{\epsilon^{-1} M} + \left( r_i u^i + h \right) \frac{\partial}{\partial A} + \frac{1}{2} d^{ij} r_i r_j \frac{\partial^2}{\partial A^2} + d^{ij} r_i \frac{\partial^2}{\partial A \partial x^i} \right] f \rangle \quad (C.6)$$

from which eq. (176) follows.

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